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Editorial

Nitrogen Mustard Therapy

THE leukopenia following exposure to mustard gas which Krumbhaar[1] described in 1919 attracted little interest. The nitrogen mustards of World War II, on the other hand, received considerable attention. It was demonstrated that the biological effects of these compounds parallel and are in many respects identical with those of roentgen rays.[2] A cytotoxic effect is produced which is closely related to the proliferative activity of tissues and this is particularly marked upon the hemopoietic tissue. A logical outcome of these investigations has been the clinical trial of certain of the nitrogen mustards in cases of neoplastic disease, especially the malignant processes involving chiefly the lymph nodes and bone marrow.

The action of the mustards depends upon intramolecular cyclization with the formation of a series of ethylene imonium compounds. The latter are highly reactive and are capable of alkylating a large number of biologically functional groups such as sulfhydryl, carboxyl and many others. The cytotoxic action probably is the result of the inactivation of one or more cellular enzymes.

Even minimally effective doses produce a striking inhibition of mitosis. Resting cells and cells in active mitosis are not appreciably affected but cells in the premitotic phase are arrested at that stage. Larger doses lead to nuclear fragmentation and dispersal of chromatin.[3] There is no evidence that there is a difference in the toxicity for malignant as opposed to normal tissue. Nevertheless, the mustards, especially methyl bis (β-chloroethyl) amine hydrochloride (HN_2), appear to be useful therapeutic agents.

Promising results have been observed in Hodgkin's disease, lymphosarcoma, chronic myelocytic and chronic lymphocytic leukemia and in polycythemia rubra vera.[4–8]

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The results in the first of these have been particularly impressive. The effect on the fever is pronounced and reduction in the size of enlarged lymph nodes and spleen, relief of symptoms due to pressure and a general sense of well being follow therapy. In a number of subjects "resistant" to x-ray therapy, remissions have been induced by nitrogen mustard therapy. It is not clear whether the remissions following treatment with HN_2 are as long as those which may be observed after roentgen therapy. Some hold that nitrogen mustard should be reserved for those patients in whom systemic involvement is extensive, local involvement being best treated by roentgen therapy. Whatever the final answer to these unsettled points may be, there can be no doubt that the introduction of the nitrogen mustards represents a therapeutic advance in the management of Hodgkin's disease. For the treatment of this disease, HN_2 is clearly superior to radioactive phosphorus.[9]

There is no good evidence that nitrogen mustard is more effective in the treatment of the lymphosarcomas or the leukemias than is roentgen therapy. It has been found, however, that HN_2 is a useful agent for the management of these disorders and the drug compares favorably with other available forms of treatment. It is perhaps but a matter of availability or convenience whether roentgen therapy or nitrogen mustard is used in a given case. Urethane is still too new for a comparison to be made. No study has been reported in which one of the radioactive isotopes has been compared with HN_2 but what evidence there is suggests that the latter may be the superior therapeutic agent. As to the acute leukemias, the best that can be said is that only very temporary alterations have been produced by the use of nitrogen mustard. Relief of bone pain has been helpful in some instances, however.

Although extensive cellular damage may be produced by the nitrogen mustards if large enough doses are given, the amounts used therapeutically (0.1 mg. per Kg. body weight, repeated three to six times in a course) produce evidence of toxic effects only in two systems, the gastrointestinal and the hemopoietic. Nausea and vomiting almost invariably follow the first injections of each course. The intensity of these symptoms varies greatly. As compared with similar symptoms accompanying roentgen therapy, their duration is often more brief even though their severity may be greater.

A reduction in the leukocyte count is frequently encountered with nitrogen mustard therapy. Both granulocytes and lymphocytes are affected. There may be a variable decrease in red cells as well as in platelets. Care must be taken to prevent the development of the agranulocytic syndrome and serious bleeding can occur although both of these complications have been quite rare. Recovery from these effects on the blood occurs in three or four weeks. Anemia, if present prior to therapy, has been relieved in those subjects responding favorably to therapy. Thus in chronic leukemia a fall in the leukocyte count has often been followed by a decrease in anemia or its complete disappearance.

Of chief importance in relation to the introduction of the nitrogen mustards, however, is the fact that an almost infinite variety of beta-halogenated amines can be prepared. Consequently, the discovery of chemical agents which possess an action like that of roentgen rays offers hope that compounds can be devised which will have a selective action on neoplastic tissue and yet will produce relatively little damage to normal tissue.

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Clinical Studies

Endocrine Changes Associated with Laennec's Cirrhosis of the Liver*

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ALTHOUGH many papers have been written on cirrhosis of the liver, not much attention has been given to the not uncommonly associated endocrine changes, chief of which are gynecomastia, atrophy of the testes, menstrual disturbances, sterility, impotence and decrease in axillary hair. The results of investigations of the rôle of the liver in steroid metabolism and the endocrine disturbances in cirrhosis of the liver may therefore be of interest. Seventy-one unselected patients with Laennec's cirrhosis of the liver were studied with particular reference to endocrine abnormalities.

REVIEW OF CLINICAL STUDIES

Silvestrini[1,2] first reported gynecomastia and Corda[3] first described testicular atrophy associated with cirrhosis, so that the triad of gynecomastia, testicular atrophy and Laennec's cirrhosis is sometimes referred to as "The Silvestrini-Corda Syndrome." Eppinger[4] added loss of axillary hair to this triad. Jacob[5] considered this latter change so characteristic of cirrhosis of the liver that he hesitated to make the diagnosis in its absence.

Impotence and loss of libido have been found by Eppinger,[6] Ratnoff and Patek[7] and Bean[8] to be present not infrequently in males with cirrhosis of the liver.

The vascular arterial "spider" may be the result of endocrine changes since Bean[9] has been able to produce "spiders" by the administration of estrogen.

Changes in the menstrual pattern have been observed by Rolleston,[10] Paisseau and Oumansky,[11] Ratnoff and Patek,[7] Laignal-Lavastine, Troisier and Boquien,[12] Bean,[8] Hartwell-Johnson.[13] These changes usually consist of menorrhagia, postmenopausal bleeding and occasionally amenorrhea.

Silvestrini[1] first explained gynecomastia associated with cirrhosis as being due to an increased collateral circulation through the breast or to abnormal substances which were not removed from the blood stream by the damaged liver. Del Guerra[14] agreed with this view. Corda[3] believed that an endocrine imbalance was the cause of gynecomastia and testicular atrophy. Silvestrini[2] later suggested that the breast changes were not true gynecomastia, but rather a chronic inflammation, at least in some cases. The hypotheses of Bolaffi,[15] Cioni[16] and Pellegrini[17] are in accord with this.

Boccia[18] believed that alcohol had a specific toxic effect on the testes and that those patients with gynecomastia and testicular atrophy have a latent hereditary predisposition to hermaphroditism which becomes apparent when unknown circulating substances depress the masculine elements in their endocrine system. Boccia,[18] as well as Pende,[19] Paula,[20] D'Antona,[21] Tobler,[22] Zanalda[23] and Manai[24] believed that testicular failure was the primary cause of gynecomastia.

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Riebler[25] has advanced the novel theory that ingestion by individuals with chronic alcoholism of large quantities of milk, a supposedly feminine substance, is an etiologic agent in gynecomastia. Menville[26] suggested that gynecomastia in patients with cirrhosis may be due to a cerebral lesion and that these patients represent mild cases of Wilson's disease (tetanoid chorea). Paula[19] also considered that the nervous system may be implicated, perhaps through involvement of the nervous factors controlling sexual processes.

Edmondson, Glass and Soll[27,28,29] have offered a more satisfactory explanation of gynecomastia which is based on the observation that breast changes are similar to those which follow experimental estrogen stimulation. Eight of fourteen men with cirrhosis had gynecomastia and were found to excrete large amounts of free and small quantities of conjugated estrogens.[27,28] They also had low urinary androgen excretions. Approximately 85 per cent of estrogen injected into patients with cirrhosis was recovered. In three patients most of the urinary estrogen was conjugated but in the fourth, who had more severe liver failure, the estrogen was mainly in a free form.[29]

Gilder and Hoagland[30] have recently studied estrogen excretion in young men suffering from acute infectious hepatitis. These authors found that during the phase of greatest liver damage there was an increased urinary excretion of estrogen and a decrease of ketosteroids. Recovery from this liver disease was followed by a return to normal of the urinary excretion of these steroids. Menstrual disorders have also been observed in female patients with infectious hepatitis.[31]

Testicular atrophy was found at autopsy by Morrione[32] in 57 per cent of twenty-eight patients with cirrhosis. He concluded that long-standing liver damage is necessary to produce this change and that the amount of atrophy is roughly proportional to the extent of liver damage. Experimental confirmation of these autopsy findings was obtained by production of much more severe testicular damage following estrogen administration to rats with damaged livers than in normal animals. A depression of the function of normal testes by estrogens has been demonstrated.[33,34]

Wu[35] found decreased involution and nodular hyperplasia of the prostate in ten of eleven men who died of cirrhosis, whereas in the same age group only 50.5 per cent of the patients who died from other causes exhibited these changes. Metaplasia of the urethral epithelium similar to that produced in rats by estrogen administration was also seen.

A few studies of pathologic changes in the entire endocrine system have been made. Barrelet[36] found testicular atrophy in 78 per cent of male patients with cirrhosis. He observed no characteristic changes in the ovaries, adrenals or pancreas of female patients. Seventy-nine per cent of his patients showed a basophilic granulation of the thyroid colloid; a decrease in size of the thyroid gland was present in 31 per cent. No constant changes could be seen in the pituitary glands. Although 28 per cent had an increase in the basophilic cells, 25 per cent had an increase in chromophobe cells. Fittipaldi[37] reported lesions similar to those seen by Barrelet and also described pancreatic changes. This author suggested that these abnormalities were due to coincidental disease and were not related to the cirrhosis. In a case of cirrhosis with gynecomastia, Capriglione, Berardinelli and daCosta Cruz[38] found a considerably increased number of basophil cells in the pituitary. Boccia[18] reported testicular atrophy and decreased function of the adrenal glands.

Many studies indicate that the liver plays an important rôle in the normal organism in the intermediate metabolism of the sex steroids. Some of the results are reviewed in the following section.

REVIEW OF ANIMAL STUDIES

Only a very small proportion of estrogen injected into the rat could be recovered from the urine, feces or carcass by Dingemanse

and Laqueur.[39] This suggested the presence in the body of a very efficient mechanism for destroying or inactivating estrogen. Evans and Burr[40] demonstrated that less estrogenic effect was produced by the intraperitoneal injection of ovarian hormones than by subcutaneous injection. Silberstein, Engel and Molnar[41] and Zondek[42] showed that liver inactivates estrogen *in vitro*.

Parker and Tenny[43] found more estrogen in human maternal and fetal livers than in any other tissue. They were unable to demonstrate a significant increase in the estrogen content of cirrhotic livers.[44]

Many studies have indicated that the liver inactivates estrogen. Perfusion of the heart-lung and heart-lung-liver preparations has demonstrated that the greatest destruction of estrogen occurred when the perfusate passed through the liver.[45] One frequently used experimental technic has been the comparison of the effects on the genital organs of estrogens which have circulated through the liver with the effects of estrogens which have by-passed the portal circulation.[46–60] From these data it can be concluded that synthetic as well as naturally occurring estrogens are inactivated by the liver *in vivo* although the former are not inactivated as rapidly as the latter. Zondek and Sklow[61] have demonstrated that this function is not influenced by the reticulo-endothelial system.

In vitro technics have also demonstrated inactivation of estrogens by the liver. Shaking with liver pulp inactivates natural[41,42] and synthetic estrogens,[62] although twice as much liver is required to inactivate diethylstilbestrol as to inactivate estrone. Twombly and Taylor[63] report that human liver slices do not have as marked capacity to inactivate estrogens as do slices of rat liver. No correlation was found between the estrogen inactivating ability of the liver and the presence or absence of cancer. Heller[64] has demonstrated that inactivation of estrogen by liver slices depends upon at least two enzyme systems. Estradiol (dihydroxyestrin) is reduced to an estrogen having the activity of estriol (the trihydroxy form). Addition of cyanide to the medium prevents this action presumably through poisoning of an oxidative enzyme. Estrone is also changed by liver slices to an estrogen having the activity of estriol. Addition of cyanide results in the formation of an estrogen similar in activity to estradiol. It would seem, therefore, that a reducing enzyme system causes the conversion of estrone to estradiol and that an oxidative system changes this more potent estrogen to the less potent trihydroxy form, estriol. This work is in agreement with the finding by Segaloff[53] that the point of attack seems to be the OH group, since substitution of this group affords partial protection against inactivation. Schiller and Pincus[65,66] have perfused rat organs with estrogens and have reached the conclusion that estradiol and estrone are interconvertible and both can be excreted as estriol. This is the generally accepted hypothesis concerning the path of estrogen metabolism in the human.[67]

Injury of the liver by poisoning with carbon tetrachloride,[68,69] or partial hepatectomy,[70] results in a decreased ability of the liver to inactivate estrogen. Production of liver injury by dietary deficiency has led to the study of the effects of diet on estrogen metabolism. Estrogen therapy in the human has been reported to increase the need for the vitamin B complex[71] or to decrease its utilization.

Dietary deficiency decreases the ability of the liver to inactivate either endogenous or exogenous estrogens. Biskind and Biskind[72–74] have reported decreased inactivation in animals deficient in the vitamin B complex, specifically riboflavin and thiamine. This work has been confirmed by Segaloff and Segaloff[75] who also found that these vitamin deficiencies caused a reduction in response to subcutaneously injected estrogen, presumably due to end-organ refractoriness. Shipley and Gyorgy[76] found that yeast corrected the decreased ability to inactivate estrogen in animals with liver injury resulting from a protein-deficient diet. However, the paired feeding experiments of Drill and Pfeiffer[77] showed that a comparable degree of inanition in rats receiving plenty of vitamin B complex resulted in a decrease of the

ability of the liver to inactivate estrogens commensurate with that found in animals on vitamin B deficient diets.

Singher et al.[78,79] demonstrated that defective inactivation of estrogen resulting from riboflavin and thiamine deficiency could be corrected by methionine. These authors suggested that a direct relationship exists between dietary protein intake and riboflavin storage. Liberal amounts of dietary riboflavin were not retained when the protein intake was low.

Decreased ability to inactivate estrogens has recently been used to estimate liver injury due to dietary deficiency in experimental animals.[80] Clinical application of the relation of vitamin deficiency to decreased estrogen inactivation has been made by Biskind, Biskind and Biskind,[81,82] who have reported inprovement with B vitamin complex therapy in disorders possibly due to excessive estrogenic activity resulting from inadequate inactivation. Ayre and Bauld[83] have described changes in the estrogen metabolism and vitamin excretion of female patients with carcinoma and functional uterine bleeding.

Androgens have also been shown to be inactivated by the liver and vitamin B deficiency was not found to decrease this effect.[57,84,85]

The work reviewed so far has dealt with the "inactivation" of estrogens by the liver. "Inactivation" by the liver is not the only means by which steroid hormones are removed from the circulation. Longwell and McKee[86] showed that following injection of estrone into dogs, estrogen of a different type, non-ketonic, was recoverable from the bile. Cantarow, Paschkis, Rakoff and associates[87–91] have also recovered estrogen and androgen from bile. They state that biliary excretion is the avenue of egress from the body and that the liver does not "inactivate" estrogen. Emery and Joyce[92] found that severance of the bile ducts increased the duration of effect of diethylstilbestrol and estrone. Morrione[32] reported less damage to the testes of the rats receiving estrogen when the bile ducts were ligated than when the liver was injured by carbon tetrachloride. He believed, therefore, that failure of inactivation of estrogens was more important than decreased excretion in the bile in causing testicular atrophy.

The possibility that estrogens may influence the course of liver injury must be considered. Although Roberts et al.[93] were not able to demonstrate any changes in glycogen, fat or nitrogen in the livers of normal dogs receiving diethylstilbestrol or estradiol, Taurog[94] and co-workers reported that diethylstilbestrol increases the incorporation of inorganic phosphorus into phospholipid in the liver. Allen's[95] observation that administration of estrogen plus progesterone induces an increased number of binucleated cells in the rabbit liver, whereas castration decreases them, suggests that the high steroid level in patients with cirrhosis may influence repair of the liver.

Szego and Roberts[96] reported that approximately two-thirds of the circulating blood estrogen is bound to protein. In view of this observation, the marked abnormalities of protein formation and metabolism seen in hepatic cirrhosis may be considered as contributing to the alteration of estrogen metabolism observed in these patients.

PLAN OF STUDY

Patients with cirrhosis of the liver, diagnosed by history, physical examination and laboratory tests, were examined for changes in endocrine function.

In most of the patients estimations were made on the serum or plasma of the icterus index, cephalin flocculation, formol gel, total protein and prothrombin. In many of the patients urine urobilinogen, serum bilirubin and serum albumin and globulin levels and thymol turbidity and bromsulphthalein retention tests were done. For the latter test 5 mg. of the dye per Kg. of body weight was administered and the amount of dye in the serum was estimated at five- and forty-five-minute intervals thereafter. Alkaline phosphatase concentrations were occasionally determined.

The history, physical findings, laboratory data and clinical course have been reviewed by Dr. Franklin White who has classified the cirrhosis into three groups: (1) "mild," (2) "moderate,"

(3) "severe." The clinical impressions of the observer, of which Dr. White was ignorant when he reviewed the data, agreed closely with his classification.*

The endocrine changes searched for were abnormalities in libido, potency, body hair, breast development, menses, prostatic size and testicular size. The frequency and severity of some of these changes are shown in Table 1. In males with testicular atrophy spermatozoa counts were attempted during part of the study but because of the complete loss of libido and potency as well as lack of cooperation, it was soon found that it was almost impossible to obtain seminal specimens. However, enough samples were obtained to indicate that decreases in testicular size and turgor were associated with a decreased function of the seminiferous tubules.

Gynecomastia was considered to be present when there was felt a firm disc of tissue with well demarcated borders and a centrally placed nipple. Cords of glandular elements could often be made out in this hyperplastic tissue. In a few cases the physical findings were checked by biopsy; in no instance did the histologic finding fail to reveal gynecomastia. Criteria for histologic diagnosis of gynecomastia were those given by Karsner.[97] Typical biopsy sections are reproduced in the photomicrographs in Figures 1 and 2. The amount of gynecomastia was roughly graded into four groups as shown in Table 1: group +, slight unilateral hyperplasia; group ++, moderate unilateral hyperplasia; group +++, marked unilateral hyperplasia; group ++++, bilateral hyperplasia.

Axillary hair loss was estimated on a + to ++++ basis, with + representing up to 25 per cent loss, ++ 50 per cent loss, +++ 75 per cent loss and ++++ 100 per cent loss. In fifteen patients the axillary hair was shaved and weighed and clinical estimation of hair loss was found to be accurate. In none of the males whose axillary hair was called normal was excessive body hair found and almost every one of the

TABLE 1

SUMMARY OF ENDOCRINE CHANGES IN FORTY-SIX MALES WITH CIRRHOSIS OF GRADE III SEVERITY

Age	No. of Cases	Decrease of Libido*				No Change in Libido	Libido Never Good	Decrease of Body Hair†				Gynecomastia‡				Testicular Atrophy	Testes Normal	Spider Telangiectasis	Testicular Atrophy and Gynecomastia	Testicular Atrophy without Gynecomastia	Gynecomastia without Testicular Atrophy	Testes Normal and No Gynecomastia	Gynecomastia and Decrease Axillary Hair	Decrease Axillary Hair without Gynecomastia	Normal Axillary Hair and No Gynecomastia	Gynecomastia with Decrease Axillary Hair
		+	++	+++	++++			+	++	+++	++++	+	++	+++	++++											
20 to 29	1	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	1	1	..	..	..	1	..	1		
30 to 39	2	..	..	..	..	1	1	1	..	..	..	..	..	..	1	..	2	2	..	..	1	1	1	..	1		
40 to 49	21	2	4	3	5	2	4	9	5	2	3	6	..	1	2	13	5	16	6	10	3	2	9	10	2	
50 to 59	15	1	8	2	2	1	1	2	8	..	2	4	..	1	3	12	1	12	7	7	1	..	6	6	1	2
60 to 69	5	1	1	..	..	..	2	1	1	1	2	2	..	..	1	4	1	5	3	1	..	1	3	2		
70+...	2	..	..	..	2	..	..	..	..	..	2	..	..	..	..	2	..	1	..	2	..	..	..	2		
Total	46	4	13	5	9	4	8	12	16	3	9	12	..	2	7	31	10	37	16§	20‖	5	5	19	21	4	2

* + slight decrease of libido.
++ moderate decrease of libido.
+++ severe decrease of libido.
++++ complete loss of libido.

† + 25% loss of body hair.
++ 50% loss of body hair.
+++ 75% loss of body hair.
++++ 100% loss of body hair.

‡ + slight unilateral gynecomastia.
++ moderate unilateral gynecomastia.
+++ marked unilateral gynecomastia.
++++ bilateral gynecomastia.

§ 2 of these patients had testes which could not be measured because of edema of scrotum.
‖ 3 of these patients had testes which could not be measured because of edema of scrotum.

* The three grades of cirrhosis were characterized by the following features: (1) *Mild*—No ascites; no definite icterus; bromsulphthalein less than 20 per cent after forty-five minutes; cephalin flocculation less than 2+. (2) *Moderate*—Icterus (spider telangiectases); collateral portal circulation; moderate amount of urobilinogen in urine; low serum protein; bromsulphthalein 20 to 40 per cent retention; cephalin flocculation 3+ or more; formol gel 2+ or more; no ascites. (3) *Severe*—Ascites (all cases); bleeding; delirium; coma; splenomegaly; icterus index 50+; low serum protein; bromsulphthalein more than 40 per cent retention; cephalin flocculation 4+; formol gel more than 3+.

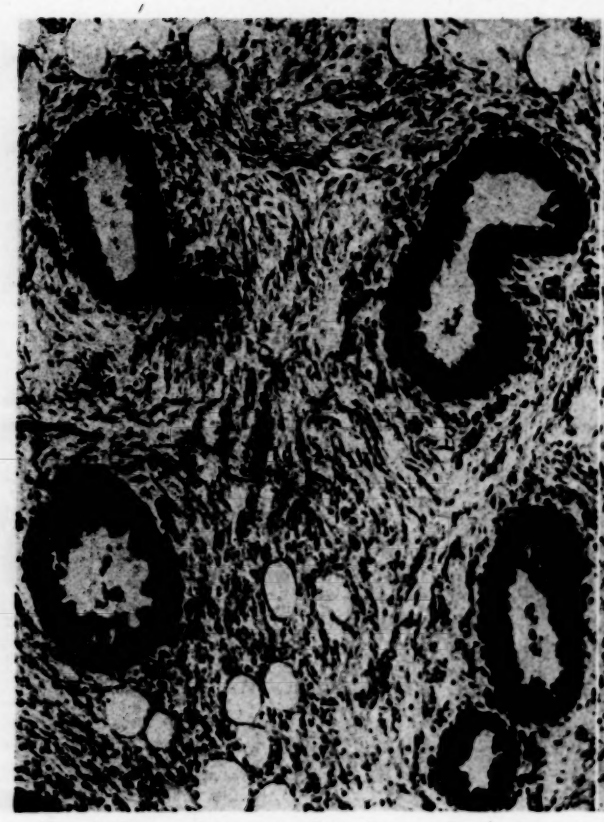


FIG. 1. Photomicrograph of the breast of a male patient, aged forty-four, with grade II cirrhosis and bilateral gynecomastia. Note marked hyperplasia of duct epithelium as well as evidence of stimulation of interstitial tissue.



FIG. 2. Photomicrograph of the breast of a male patient, aged forty-two, with grade III cirrhosis and bilateral gynecomastia. Following testosterone propionate as well as adequate dietary therapy for the liver disease, gynecomastia completely disappeared.

patients stated that he had never had much body hair.

Testicular size was determined in three dimensions. Testes under 4.5 by 2.5 by 2.5 cm. were considered decreased in size. The normal measurements for testes cited in Gray's Anatomy[98] are 4 to 5 cm. by 2.5 cm. by 3 cm. Since the thickness of the scrotum is also included in our measurements, we have made our lower limits of normal slightly higher than those given for the uncovered testis. The testes of ten normal males all had greater dimensions than the above figures.

Estimations of the size of the prostate varied considerably so that these figures are not very satisfactory. However, it can be said that the size was comparable to that of similar age groups of individuals without cirrhosis.

The breasts of all female patients were carefully examined for nodules and an estimation of the amount of glandular tissue was made.

Careful menstrual histories were taken of all women. Two patients in the reproductive age group had endometrial biopsies.

RESULTS IN MALES

Libido and Potency. Of two patients with grade I cirrhosis, one had a definite but slight decrease in libido. The other had always had a subnormal libido and had noted no change with the development of cirrhosis. Neither patient reported any change in potency.

Five of seven patients with grade II cirrhosis had a marked decrease in libido and two of the five had decreased potency. One patient had never had much libido and he could notice no change. The seventh had normal libido and potency.

A total of forty-six patients with grade III cirrhosis were seen, but only forty-three of these could respond to questioning as three

were comatose. Thirty-one of these, or 72 per cent, had definitely decreased libido and potency. Four patients (9 per cent) had noted no change and eight (18 per cent) had never had normal sexual drive.

Decrease in libido was frequently the first symptom noted by patients with cirrhosis.

Body Hair. One of the two patients with grade I cirrhosis had a 50 per cent decrease in axillary hair, but the other one had no change.

Of the seven patients with grade II cirrhosis five had decreased axillary hair. Normal body hair was present in two.

Forty of the forty-six patients with grade III cirrhosis (87 per cent) had decreased axillary hair, but the other six patients had no change in this regard.

The decrease in axillary hair in the patients with grade III cirrhosis was of a more marked degree than in the other two groups. None of the nine individuals with grade I and II cirrhosis had ++++ hair loss and only two had +++ hair loss. Of the forty-six subjects with grade III cirrhosis the hair loss of nine was classified as ++++ and of three as +++.

Testicular Atrophy. Neither of the two patients with grade I cirrhosis had testicular atrophy.

Five of the seven subjects with grade II cirrhosis had definite testicular atrophy. Although the greatest atrophy was found in a man of seventy, atrophy was also present in four of five men under forty-two years of age.

Of the forty-six subjects with grade III cirrhosis, five had such massive scrotal edema that an accurate estimation of testicular size could not be made. Thirty-one (75 per cent) of the remaining forty-one had definite testicular atrophy. The incidence of atrophy increased *pari passu* with age; no atrophy occurred in three patients under forty years of age, but it occurred in 62 per cent of twenty-one patients in the group aged forty to forty-nine, in 80 per cent of fifteen subjects in the group aged fifty to fifty-four years and in 86 per cent of seven patients over sixty years of age.

Association of Testicular Atrophy with Axillary Hair Loss. Twenty-seven of thirty-one patients (81 per cent) with testicular atrophy had decreased axillary hair. No correlation could be found between the amount of hair loss and the degree of atrophy. Four of thirty-one patients (13 per cent) with testicular atrophy had little, if any, change in axillary hair. Conversely, of forty patients with hair loss, eight (20 per cent) had no change in the size of the testes. All five of the patients on whom no measurements were possible because of scrotal edema had decreased axillary hair.

Gynecomastia. Twenty-three of fifty-five male patients (42 per cent) had gynecomastia. In two patients with mild, or group I cirrhosis, no gynecomastia occurred. Of seven patients with group II cirrhosis there were three subjects with gynecomastia. Two of these were graded + and one was ++++. (Fig. 2.)

Twenty of forty-six patients with grade III cirrhosis had gynecomastia. Twelve of these were classified as +, two as +++ and seven as ++++. One additional patient with grade III cirrhosis was found to have had definite gynecomastia two years previously. At that time he had severe liver decompensation with ascites and icterus. In association with a regimen of high vitamin and high caloric diet and abstinence from alcohol the gynecomastia disappeared.

One of the patients with ++++ gynecomastia developed this condition while he was in the hospital three months after being admitted in cholemic coma. A photomicrograph of one breast biopsy is shown in Figure 1. Following biopsy, the patient was given testosterone propionate in oil intramuscularly, 75mg. per week for two months. During this interval the patient received the usual form of therapy, i.e., high caloric, high protein, high vitamin diet and he made a good recovery with disappearance of ascites and icterus. A subsequent biopsy of the breast showed subsidence of the gynecomastia and later physical examinations revealed normal breasts. This patient had not had any libido for several months and he

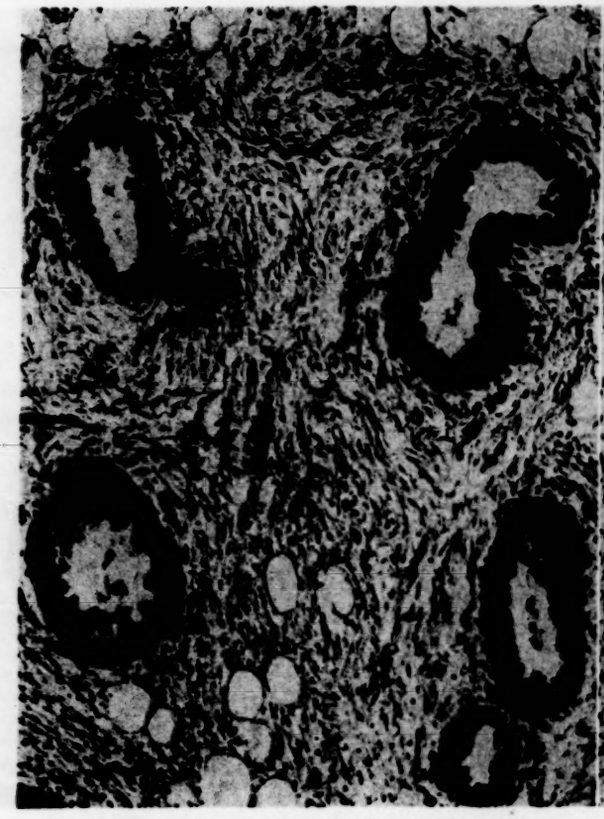


FIG. 1. Photomicrograph of the breast of a male patient, aged forty-four, with grade II cirrhosis and bilateral gynecomastia. Note marked hyperplasia of duct epithelium as well as evidence of stimulation of interstitial tissue.



FIG. 2. Photomicrograph of the breast of a male patient, aged forty-two, with grade III cirrhosis and bilateral gynecomastia. Following testosterone propionate as well as adequate dietary therapy for the liver disease, gynecomastia completely disappeared.

patients stated that he had never had much body hair.

Testicular size was determined in three dimensions. Testes under 4.5 by 2.5 by 2.5 cm. were considered decreased in size. The normal measurements for testes cited in Gray's Anatomy[98] are 4 to 5 cm. by 2.5 cm. by 3 cm. Since the thickness of the scrotum is also included in our measurements, we have made our lower limits of normal slightly higher than those given for the uncovered testis. The testes of ten normal males all had greater dimensions than the above figures.

Estimations of the size of the prostate varied considerably so that these figures are not very satisfactory. However, it can be said that the size was comparable to that of similar age groups of individuals without cirrhosis.

The breasts of all female patients were carefully examined for nodules and an estimation of the amount of glandular tissue was made.

Careful menstrual histories were taken of all women. Two patients in the reproductive age group had endometrial biopsies.

RESULTS IN MALES

Libido and Potency. Of two patients with grade I cirrhosis, one had a definite but slight decrease in libido. The other had always had a subnormal libido and had noted no change with the development of cirrhosis. Neither patient reported any change in potency.

Five of seven patients with grade II cirrhosis had a marked decrease in libido and two of the five had decreased potency. One patient had never had much libido and he could notice no change. The seventh had normal libido and potency.

A total of forty-six patients with grade III cirrhosis were seen, but only forty-three of these could respond to questioning as three

were comatose. Thirty-one of these, or 72 per cent, had definitely decreased libido and potency. Four patients (9 per cent) had noted no change and eight (18 per cent) had never had normal sexual drive.

Decrease in libido was frequently the first symptom noted by patients with cirrhosis.

Body Hair. One of the two patients with grade I cirrhosis had a 50 per cent decrease in axillary hair, but the other one had no change.

Of the seven patients with grade II cirrhosis five had decreased axillary hair. Normal body hair was present in two.

Forty of the forty-six patients with grade III cirrhosis (87 per cent) had decreased axillary hair, but the other six patients had no change in this regard.

The decrease in axillary hair in the patients with grade III cirrhosis was of a more marked degree than in the other two groups. None of the nine individuals with grade I and II cirrhosis had ++++ hair loss and only two had +++ hair loss. Of the forty-six subjects with grade III cirrhosis the hair loss of nine was classified as ++++ and of three as +++.

Testicular Atrophy. Neither of the two patients with grade I cirrhosis had testicular atrophy.

Five of the seven subjects with grade II cirrhosis had definite testicular atrophy. Although the greatest atrophy was found in a man of seventy, atrophy was also present in four of five men under forty-two years of age.

Of the forty-six subjects with grade III cirrhosis, five had such massive scrotal edema that an accurate estimation of testicular size could not be made. Thirty-one (75 per cent) of the remaining forty-one had definite testicular atrophy. The incidence of atrophy increased *pari passu* with age; no atrophy occurred in three patients under forty years of age, but it occurred in 62 per cent of twenty-one patients in the group aged forty to forty-nine, in 80 per cent of fifteen subjects in the group aged fifty to fifty-four years and in 86 per cent of seven patients over sixty years of age.

Association of Testicular Atrophy with Axillary Hair Loss. Twenty-seven of thirty-one patients (81 per cent) with testicular atrophy had decreased axillary hair. No correlation could be found between the amount of hair loss and the degree of atrophy. Four of thirty-one patients (13 per cent) with testicular atrophy had little, if any, change in axillary hair. Conversely, of forty patients with hair loss, eight (20 per cent) had no change in the size of the testes. All five of the patients on whom no measurements were possible because of scrotal edema had decreased axillary hair.

Gynecomastia. Twenty-three of fifty-five male patients (42 per cent) had gynecomastia. In two patients with mild, or group I cirrhosis, no gynecomastia occurred. Of seven patients with group II cirrhosis there were three subjects with gynecomastia. Two of these were graded + and one was ++++. (Fig. 2.)

Twenty of forty-six patients with grade III cirrhosis had gynecomastia. Twelve of these were classified as +, two as +++ and seven as ++++. One additional patient with grade III cirrhosis was found to have had definite gynecomastia two years previously. At that time he had severe liver decompensation with ascites and icterus. In association with a regimen of high vitamin and high caloric diet and abstinence from alcohol the gynecomastia disappeared.

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developed none during the time that he received testosterone. Four months after the last injection of testosterone, when the patient's general condition was excellent, he noted a slight return of libido but diminished potency persisted. The spermatozoa count at this time was 7,000,000 per cc. with a total count of 14,000,000. Only 45 per cent of the spermatozoa were motile.

Association of Gynecomastia with Other Endocrine Changes. In twenty-one of twenty-three patients with gynecomastia there was a definite decrease in axillary hair. The patient who is reported as having had gynecomastia on a previous admission, but whose breasts were normal following several years of good liver compensation, also had decreased axillary hair.

Definite testicular atrophy was present in sixteen of twenty-one patients with gynecomastia (76 per cent) in whom the testes could be measured. In two other patients with gynecomastia the testes could not be measured due to scrotal edema. Five (24 per cent) of the patients with gynecomastia were not thought to have testicular atrophy.

All but one of twenty-three patients with gynecomastia had decreased libido.

Androgen and 17-ketosteroid Excretion. Four male patients with severe (grade III) cirrhosis were studied for alterations in androgen and 17-ketosteroid excretion. The free and combined 17-ketosteroids excreted in complete pooled three-day urine collections were determined. The urine was extracted with carbon tetrachloride. The extract was purified with Girard reagent and the amount of color formed with metadinitrobenzene was measured. Free and total androgen excretion was determined by the method of Rakoff, Paschkis and Cantarow,[99] using the comb weight changes in the chick following application once daily for seven days of an ether solution of the androgen to the comb. The androgen assay results are not considered as absolute but are reported simply because they indicate a trend.

After a three-day control period, each patient received 50 mg. intramuscularly of testosterone propionate, following which another three-day complete urine collection was assayed for 17-ketosteroids and androgens. As can be seen in Table II only a small amount of 17-ketosteroids was excreted before injection of testosterone and there was no increase after injection. No free androgen was detectable in any of the specimens assayed; therefore only the total androgen values are tabulated.

TABLE II

AVERAGE TWENTY-FOUR-HOUR URINARY ANDROGEN AND 17-KETOSTEROID EXCRETION FOR THREE-DAY PERIODS BEFORE AND AFTER THE INJECTION OF 50 MG. OF TESTOSTERONE PROPIONATE (EXPRESSED AS MG. OF ANDROSTERONE)

	Before			After		
Cirrhosis of the Liver						
	Andro-gen	17-ks. Free	17-ks. Total	Andro-gen	17-ks. Free	17-ks. Total
V.....	10	.36	2.8	0	.29	2.6
G.....	3.9	0	.61	32.3	.64	3.9
B.....	22.2	.26	1.5	59.3	.402	3.8
M.....	46	0	5.6	54.2	.025	5.8
Carcinoma of Common Bile Duct with Biliary Fistula						
Bile....	0	....	....	0		
Urine..	6.5	....	....	46.3		

The increase of androgenic activity and failure of increase of 17-ketosteroids following injection of testosterone is at variance with results reported for normal males[100] in whom from 14 to 70 per cent of the testosterone injected has been recovered from the urine as 17-ketosteroids.

In Table II is also shown the amount of androgen excreted in bile and urine after 50 mg. of testosterone propionate was administered to a woman, age seventy-two, with carcinoma of the bile duct and a biliary fistula. This patient was icteric but had normal cephalin flocculation test, prothrombin time and serum protein level. The serum alkaline phosphatase level was elevated. Very little biliary excretion of 17-ketosteroids or of steroids having androgenic ac-

tivity was found but a considerable increase in urinary androgen excretion occurred following injection of testosterone. In this patient the small amount of androgen excreted in the bile was perhaps due to impairment of liver function indicated by the

RESULTS IN FEMALES

Sixteen female patients with cirrhosis are included in this series. Four of these patients, one in group II and three in group III, had been oöphorectomized many years before the development of cirrhosis. These patients

TABLE III

SUMMARY OF CHANGES IN SIXTEEN FEMALE PATIENTS WITH CIRRHOSIS

Grade of Cirrhosis	Age	No. of Cases	Amenorrhea	Menstrual Change			Decrease in Axillary Hair				Breast Changes		Pelvic Changes		Spider Type of Telangiectasis
				Cyclic Decreased Flow	Irregular Bleeding		+	++	+++	++++	Atrophy	Nodules	Atrophy	Enlargement of Uterus	
					Meno-metrorrhagia	Infrequent Bleeding. Normal Flow									
I	51	1	..	..	..	1	1	..	..	..	1	..	..	..	1
II	28														
	40†	2	..	1	..	..	..	..	..	..	1	..	..	..	1
	38	1	..	..	..	..	..	..	..	1	1				
III	32–38	4	..	..	2	1	..	1	..	..	2	1	..	1	3
	41–45	4	2	..	1	1	1	1	..	2	3	..	2	..	3
	47–50*	3	3	..	..	..	2	..	..	1	3	..	..	..	1
	78	1	1	..	..	..	..	..	..	1	1	..	1	..	1
Total.....	.....	16	6	1	3	3	4	2	..	5	12	1	3	1	10

* These patients had had an oöphorectomy.
† This patient had hirsutism.

elevated serum alkaline phosphatase. If this be the case, the ability of the liver to excrete steroid substances in the bile must be extremely sensitive to minor derangements of liver function since this patient had changes in liver function of insufficient severity to cause alteration in the cephalin flocculation test, the prothrombin time or the serum proteins.

Gonadotrophin Excretion. In three male patients with cirrhosis and well developed gynecomastia, the urine was assayed for the follicle stimulating hormone. Each of the subjects excreted less than 5 rat units per 24 hours. Whether a smaller amount than normal was excreted is not known.

all had atrophic changes characteristic of absent ovarian function and had no evidence of estrogenic activity. All of these patients had decreased axillary hair. (Table III.) Only one of them had spider telangiectases and in this patient they were small and few.

One of the four oöphorectomized patients was found at autopsy to have changes in the breasts similar to those seen in gynecomastia in the male which were quite different from the simple atrophy usually seen in the castrated female. No explanation was found although the adrenals were carefully studied:

The one female patient with grade I cirrhosis was fifty-one years of age. Her men-

strual cycle had become irregular during the previous year. Pelvic examination showed that the genitalia were normal. The body hair was slightly decreased; the breasts were flabby but otherwise not remarkable.

One of two patients with cirrhosis of grade II severity was twenty-eight years of age. She still had cyclic menstrual bleeding and had no changes attributable to endocrine abnormality. The other individual was forty years of age. She had evidenced no definite change in libido. Definite facial and abdominal hirsutism had been present for three years but no virilization. There was no decrease in axillary hair. The menstrual periods were still cyclic but the duration and amount of bleeding had decreased. The breasts were small. Steroid excretion studies were not made in this patient so that the possibility that she might have had adrenal hyperplasia was not determined.

Of nine patients with cirrhosis of grade III severity, one was seventy-eight years of age and as far as could be ascertained had a normal climacteric some thirty years previously. She showed senile atrophy of the breasts and genitalia with complete loss of axillary hair. Although this patient had obviously had little or no ovarian function for many years, she had numerous small spider telangiectases.

Of the remaining eight women with grade III cirrhosis, seven had menstrual irregularities of various types. Two patients, forty-four and forty-five years of age, had amenorrhea for four months and one year respectively. The second of these patients had had menometrorrhagia for approximately one year before her menopause. A third patient, aged thirty-eight, had amenorrhea for eight months when first examined. At this time endometrial biopsy showed an extremely atrophic endometrium. Following adequate therapy with good compensation of liver function, this patient again began to have cyclic menstrual periods. Unfortunately, it was not possible to get another endometrial biopsy. One other patient with severe cirrhosis had infrequent bleeding with a normal amount of bleeding at each period. The three remaining patients with menstrual changes had excessive bleeding. One of these patients required dilatation and curettage of the uterus. The endometrium was extremely hyperplastic.

These patients had other endocrine alterations associated with their menstrual changes. Five of the eight had decreased axillary hair; five had atrophy of the breasts. A sixth patient who had menometrorrhagia, uterine enlargement and a hyperplastic endometrium had numerous large nodules in both breasts. A clinical diagnosis of chronic cystic mastitis was made but no biopsy could be obtained. Six of these eight patients had spider telangiectases.

AUTOPSY FINDINGS

Adrenals. In eighty-seven patients with alcoholic cirrhosis no striking macroscopic changes in the adrenals were observed aside from tuberculosis in three subjects and hemorrhage in two women. Some of the glands were smaller and a few were larger than normal. On microscopic examination small cortical adenomas were found in two patients, focal fibrosis in two, marked vascular congestion in four and atrophy in one. There was lumen formation in seven individuals. In fourteen women there was infiltration of the cortices with varying numbers of lymphocytes and macrophages. A distinct decrease in lipoid material was observed in most of the glands.

Pancreas. In twenty-eight of sixty-four patients examined there was fibrosis of the acinar portion of the pancreas, scarring being marked in some cases. In three instances there was hyalinization and scarring of the islets. In six subjects there were varying degrees of acute pancreatitis.

Testes. The data available do not permit an accurate evaluation of testicular lesions because microscopic sections were not taken in all cases. However, sections were made in twenty-three of fifty-six patients. There was definite atrophy of the germinal epithelium in eight with essentially no evidence of spermatogenesis. A primary carcinoma of the testis was present in one patient.

Prostate. Sections were made in twelve of the above subjects. These revealed benign prostatic hypertrophy in five patients, atrophy in one, carcinoma in one and metaplasia in one.

COMMENTS

Although much more study is needed to elucidate completely the rôle of the liver in the metabolism of steroid hormones, all available data indicate that it is an important one. It is to be expected that alterations in hormone physiology should occur in association with severe liver decompensation. This study of fifty-five male and sixteen female patients with cirrhosis of the liver has demonstrated the comparative frequency of endocrine changes among patients with this disease. The changes resulting from altered hormonal function which we observed consisted of the following: decrease in body hair, particularly of axillary hair; atrophy of the testes; decrease of libido and potency; sterility; menstrual disturbances; gynecomastia; telangiectasia and "liver" palms; decreased urinary excretion of androgens and 17-ketosteroids. Others have reported increased excretion of estrogen.[29]

In males the earliest change usually is a decrease in libido, followed soon thereafter by a decrease in potency. Decreased sexual drive is apparently related to gonadal insufficiency which is demonstrable by clinical and pathologic examination. However, it is not yet known whether the decrease in testicular function is the result of depression of the gonad by the high level of circulatory estrogen which these patients develop as a result of decreased liver function, or to a suppression of pituitary gonadotrophic hormones. Although the majority of our patients had decreased sexual drive, a considerable number had never had normal libido. This lack of heterosexual drive may well be related to the fundamental physiologic conflict which led to chronic alcoholism.

Both male and female patients were often found to have decreased axillary hair which was probably due to a lessening of adrenal activity. Other evidence also indirectly suggests decreased adrenal function. The 17-ketosteroid excretion of male patients with cirrhosis is lower than is usually found when gonadal steroid excretion alone is absent which suggests that adrenal hormone production, as well as testicular hormone formation, is less than normal. Necropsy examination of the adrenal gland shows a very low content of lipoid material. A few quantitative estimations of the cholesterol content of the adrenals have shown lower levels than are usually found in the adrenals of patients dying of chronic illnesses.[100] Electrolyte changes in patients with hepatic cirrhosis are not characteristic and alterations in carbohydrate metabolism, which might be attributed to adrenal insufficiency, are usually masked by the effects of the diseased liver. The relative lymphocytosis so frequently seen in patients with cirrhosis might possibly be the result of decreased adrenal steroid secretion. Some of the patients with liver disease who are pigmented and present a picture of "pseudo-Addison's disease" may actually have relative adrenal insufficiency.

Tepperman[102] has suggested that since the cholesterol content of the adrenal gland, which might possibly be the precursor of the cortical steroid hormones, is largely in esterified form, inability of the diseased liver to esterify cholesterol may lead to a decrease in the manufacture of adrenal hormones. Another possibility is that the high level of estrogen in the blood may depress adrenal function. This effect has been demonstrated by Hamblen, Pattee and Cuyler,[103] who found that estrogen administration was followed by a decrease in urinary 17-ketosteroid excretion, presumably due to adrenal inhibition.

Part of the estrogen in each sex is probably secreted by the adrenal gland. Although it is likely that the total amount of estrogen formed is less than in the normal individual, ability of the liver to inactivate estrogen is so much impaired that the total circulating estrogen, particularly the unconjugated or biologically active form, is increased. The

increase in free estrogen could be considered as the cause of gynecomastia, metaplasia of the prostate and testicular atrophy. In the female, breast nodules and alterations in menstrual pattern probably result from increased level of estrogen. It is possible that of many others who have found adrenal enlargement following estrogen administration or castration of male animals. It is probable that the same mechanism is at work in the production of adrenal stimulation in all of these situations. Probably

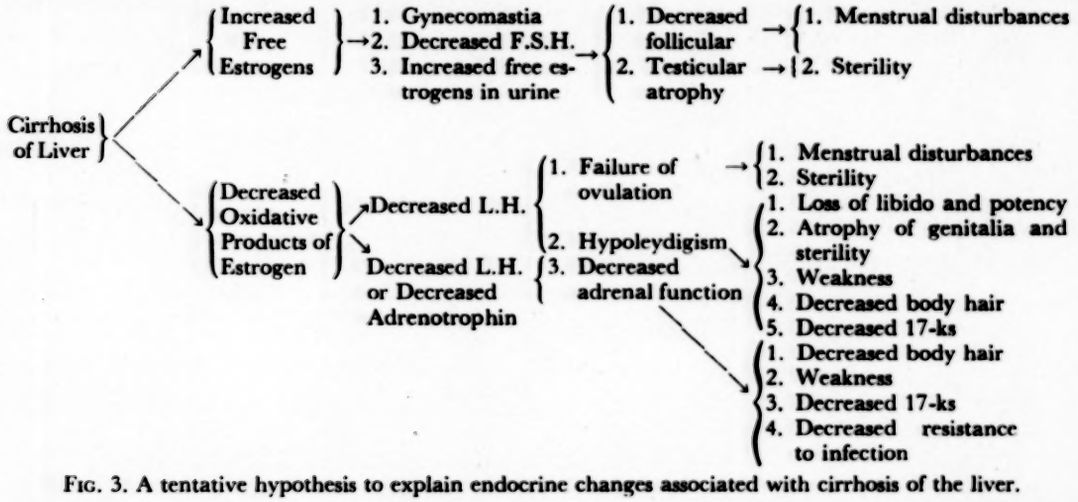


FIG. 3. A tentative hypothesis to explain endocrine changes associated with cirrhosis of the liver.

development of telangiectases in both sexes may be related to the high estrogen level.

The urinary gonadotrophin excretion was not elevated in three of our male patients. Smith and Smith[104–106] have reported that release of luteinizing hormone from the pituitary gland occurs following administration of diethylstilbestrol or of such oxidative products of estrogen as Westerfeld's[107] lactone of estrone. If this mechanism of release of luteinizing hormone obtains in the human, it might be expected that luteinizing hormone would be released from the pituitaries of patients with cirrhosis of the liver who have high circulating estrogens. However, it may be that this does not occur because the estrogen is in a free and unoxidized form since Smith and Smith have reported that it is the metabolic products of estrogen and not the estrogen *per se* which causes release of luteinizing hormone from the pituitary gland.

A tentative hypothesis to explain adrenal insufficiency in these patients could be based on the observations of Smith and Smith that the lactone of estrone causes adrenal enlargement, of Levin[108] that diethylstilbestrol causes a decrease in adrenal cholesterol and adrenotrophic hormone is released by the same stimulus that causes release of luteinizing hormone although the possibility must be considered that luteinizing hormone can stimulate the adrenal. This stimulation to the release of luteinizing hormone and of adrenotrophin is furnished by estrogenically inactive metabolic products of estrogen which are the result of one of the functions of the normal liver. The diseased liver is unable to inactivate estrogens and form these oxidative products.

The data accumulated suggest, as illustrated in Figure 3, that the liver may participate in steroid metabolism in the following manner: (1) It aids in the interconversion of estradiol and estrone and their conversion to estriol; (2) it participates in the formation of inactive oxidative products from estrogen; and (3) it conjugates estrogens for inactivation and excretion. With a marked decrease in these functions of the liver, the following sequence of changes might be expected to take place: free estrogen will accumulate in the blood and urine; associated with this there occurs a diminution in the release of follicle stimulating hormone, a suppression of spermatogenesis and follicle maturation

as well as estrogenic stimulation of target organs. The decrease in the inactive oxidative products of estrogen leads to a decreased release from the pituitary of luteinizing hormone and possibly of adrenotrophin. This, in turn, will result in menstrual abnormalities, decreased activity of the cells of Leydig and decreased adrenal function with loss of axillary hair and diminished urinary 17-ketosteroid excretion.

The foregoing explanations seem reasonable on the basis of available data. However, much more information is necessary to establish them as facts.

SUMMARY

A study has been made of endocrine functions in seventy-one patients with cirrhosis of the liver. These patients were graded I, II, and III according to the severity of their liver disease.

Fifty-five of the subjects were males and sixteen were females. Clinical endocrine changes observed in the male subjects consisted of decreased libido and potency, atrophy of the testicles, decreased body hair and gynecomastia. Telangiectasia and "liver palms" were also regarded as possibly being related to altered endocrine function.

Decrease in libido and potentia were found in thirty-seven of fifty-two (71. per cent) of the male subjects who could be questioned satisfactorily.

Decreased axillary hair was present in forty-six of the fifty-five male patients (84 per cent). Forty of the forty-six individuals with severe cirrhosis (87 per cent) had a decrease in axillary hair. The greatest decrease of body hair was found in this group.

Testicular atrophy was present in thirty-six of fifty patients (70 per cent) in whom the size of the testes was measured. Seventy-five per cent of the severe cases had atrophy of the testicles.

Gynecomastia was present in twenty-three of fifty-five patients (42 per cent).

Following injection of testosterone propionate intramuscularly, four male subjects had no increase in the quantity of 17-ketosteroid substances in the urine but two had significant increase in the total excretion of androgens.

In three male patients in whom the urinary gonadotrophin excretion was assayed no increased excretion was formed.

In the females there were alterations in menstrual pattern, sexual drive, body hair, the uterus and in other target organs of estrogen including the breast.

Seven of eight female subjects who were in the reproductive age had menstrual abnormalities. Four of these patients had amenorrhea or infrequent bleeding. There was a decrease of axillary hair, atrophy of the breasts in five of these seven patients and chronic cystic mastitis in one.

In almost all of eighty-seven patients with Laennec's cirrhosis with postmortem examinations at the Mallory Institute of Pathology there was a decrease in lipoid content of the adrenals and in eight of twenty-three patients there was atrophy of the testes.

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Complications of Alkalosis*

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IN 1945, we saw in consultation a patient who, during the course of treatment for intestinal obstruction, developed acute delirium with marked impairment of renal function. Further investigation revealed typical features of severe alkalosis. Prompt therapy with ammonium chloride was followed within a few hours by a dramatic change in the mental state and a slow but complete recovery of normal function of the kidneys. On reviewing the situation it was apparent that alkalosis had been precipitated by a combination of two factors: (1) frequent gastric lavage and (2) the administration of large amounts of sodium lactate in conjunction with the use of sulfadiazine.[1]

During the course of the next few months we had occasion to see additional similar patients with alkalosis. Of the nine patients, six exhibited both delirium and renal insufficiency, two showed delirium only and one developed renal insufficiency without mental disturbance.

CASE REPORTS

CASE I. C. S., a thirty year old white man, had a subtotal resection of his pancreas for hypoglycemia. Following the operation he was given daily intravenous injections of sodium lactate and sulfadiazine. Because of vomiting, gastric suction was started on the fifth postoperative day. He did not do well and continued to complain of nausea, vomiting, abdominal pain and headache. By the seventh postoperative day he was in a condition of semistupor. He was apathetic, lethargic, disorientated in time and place, respirations were slow and shallow and he became cyanotic. His extremities were rigid but although muscle twitching was constant the Chvostek and Trousseau signs were negative. The following day he became semicomatose and only occasionally responsive. Cyanosis increased. The carbon dioxide combining power was 106 volumes per cent, the plasma chlorides were 310 mg. and the blood urea nitrogen was 74 mg. At this time he was given 20 Gm. of ammonium chloride intravenously. Four hours later he was mentally clear and alert. He ultimately recovered completely but the blood urea nitrogen did not return to normal until the twenty-first postoperative day. The urine remained normal throughout.

CASE II. J. C., a fifty-seven year old white woman, was admitted to the Hospital because of a two day history of intestinal obstruction. An emergency exploration disclosed a loop of ileum obstructed by an adhesive band. The urine and the blood urea nitrogen were normal at that time. Following operation she was started on continuous gastric suction and was given injections of $\frac{1}{6}$ molar sodium lactate solution daily. During the first five postoperative days she gradually became more and more confused with increasing disorientation as to time, place and space. She became uncooperative, fought violently with her nurse, attempted to climb out of bed and pull out the nasal and intravenous tubes. During the sixth, seventh and eighth postoperative days she was restless, excited, disoriented and incoherent. The respirations became slow and shallow and cyanosis appeared. By the eighth hospital day her condition was critical. She was prostrate, delirious and stuporous. During the height of the delirium the urine contained +++ albumin and hyaline and granular casts. The carbon dioxide combining power was reported as "over 90." The value of chlorides in the plasma was 420 mg.

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TABLE I
CLINICAL DATA BEFORE AND AFTER TREATMENT OF ALKALOSIS

Patient	Date	Blood Serum Levels		
		CO_2, Vols. %	Blood Urea Nitrogen, Mg. %	Chlorides, Mg. %
C. S.	8/31	63		540
	9/6	106	74	310
	9/7	106	50	350
	9/7	Ammonium chloride started		
	9/17	62	21	510
J. C.	12/24	78	18	480
	12/26	90+	29	445
	12/27	90+	63	
	12/30	Ammonium chloride started		
	12/30	75	35	430
	1/11	74	13	610
J. L.	11/15	64	40	
	11/26	110	73	
	11/29	104	66	520
	11/29	Ammonium chloride started		
	12/2	87	42	500
	12/6	69	39	
P. M.	1/16		59	
	1/17	81	71	380
	1/18	76	75	420
	1/20	Ammonium chloride started		
	1/24	61	31	620
A. R.	7/3		15	
	7/16 (a.m.)	90+		349
	7/16	Gastric suction and sodium lactate discontinued		
	7/16 (p.m.)	70	33	
C. G.	6/19	100+	16	
	6/20	100+		334
	6/21	Ammonium chloride started		
	6/21	80+		378
	6/25	63	8	525
W. P.	4/15	90+		347
	4/19	90+		246
	4/19	Treatment started		
	4/20	68		485
H. H.	5/8		25	580
	5/10	Gastric aspiration discontinued		
	5/22		44	
	5/23	Alkali discontinued		
	5/25	81	61	
	6/4		33	
	10/26		24	
D. O.	2/18		22	
	3/30	90	32	
	3/31	Ammonium chloride started orally		
	4/2	66	36	578
	4/4	60	29	
	4/22	Gastroenterostomy		
	4/25	80	20	535

and the blood urea nitrogen was 63 mg. On the eighth postoperative day, gastric suction and sodium lactate were discontinued and she was given 20 Gm. of ammonium chloride intravenously. Within a few hours after the infusion there was a dramatic clearing of the sensorium and she became orientated and cooperative. Her respirations attained normal depth and frequency and the cyanosis disappeared. The remainder of the hospital course was complicated by pulmonary emboli but she eventually made a complete recovery. The urine became normal after the twelfth postoperative day, although the blood urea nitrogen remained elevated until the twenty-sixth hospital day.

CASE III. J. L., a fifty-five year old white man, was admitted to the Hospital because of unexplained intestinal obstruction. He was started on gastric suction. During the hospital course he developed mild bronchopneumonia for which he was given parenteral sulfadiazine and sodium lactate. He recovered promptly from the pneumonia but as the pneumonitis subsided he became delirious, disorientated in time and place, had visual hallucinations and was incontinent of bladder and bowel. He was facetious, assaultive and uncooperative. He repeatedly attempted to climb out of bed, pulled out infusion tubes, struck a nurse and attempted to strike a physician and a consulting psychiatrist. At the height of this mental disturbance the carbon dioxide combining power was 110 volumes per cent and the blood urea nitrogen was 73 mg. The urine showed ++ to +++ albuminuria (but no formed elements) for six days. Because of the aberrations in the blood chemical findings, the gastric suction was stopped as was the sodium lactate and he was given 4 Gm of ammonium chloride daily by mouth for five days. During the next few days the mental state cleared and he became oriented, alert and cooperative. The CO_2 combining power was normal on the fourth day. Although he subsequently died of carcinomatosis there were no other episodes of disorientation and the carbon dioxide combining power remained within normal limits.

CASE IV. P. M. was an emphysematous sixty year old white man whose renal function on a previous admission had been found to be nor-

mal. For a year he had been on a Sippy diet and had taken alkaline powders. For five months he had vomited with increasing frequency and three days before admission he vomited a large amount of bright red blood. At the time of entry to the Hospital he was found to be completely disorientated in time and place. He was drowsy, apathetic and had paranoid delusions. There was constant muscular twitching of the extremities although the Chvostek and Trousseau signs were absent. The remainder of the examination was normal. Blood pressure was 120/68 and there were no signs of vascular disease. The urine showed + albuminuria for a few days only. During the first seven hospital days he was kept on a Sippy regimen and given alkaline powders. On this program the disorientation increased and he became more apathetic and drowsy. Finally he became completely uncooperative and was incontinent of urine and feces. Muscular twitching was constantly present. At the height of this mental disturbance the carbon dioxide combining power was reported as "over 80," blood chlorides were 380 mg and the urea nitrogen was 71 mg. Treatment was then changed and he was started on venoclysis of sodium chloride and was given ammonium chloride by mouth. Within twenty-four hours the patient was completely oriented and his paranoid delusions had disappeared. The rest of his sojourn in the hospital was uneventful. An x-ray of the gastrointestinal tract revealed a duodenal ulcer without obstruction and he was discharged with complete control of his gastric symptoms. Ten months later renal function tests still showed impairment of kidney function.

Case v. A. R., a sixty-six year old physician, was admitted to the Hospital for resection of a malignant lesion of the ascending colon. Postoperatively she was started on gastric suction and given sulfadiazine and sodium lactate daily. On the fifth postoperative day she was found to be disorientated in time and place and was talking incessantly to herself. On the sixth postoperative day she was still cloudy mentally and on this day she had a severe, generalized epileptiform seizure of several minutes' duration. The following day she was found trying to climb out of bed, was very uncooperative, talked incoherently and was disorientated and irrational. She did not recognize any of her relatives, nurses or physicians and was incontinent of urine and feces. During the height of this mental disturbance the carbon dioxide combining power was reported as "over 90" and blood chlorides as 349 mg. The ECG showed a long Q-T interval. Because of these findings the sodium lactate and gastric suction were discontinued. The following day the patient was found to be mentally clear, alert, oriented and cooperative and the carbon dioxide combining power was 70 volumes per cent. The blood urea nitrogen did not rise above 33 mg. and the urine remained normal throughout.

Case vi. C. G., a forty-five year old white man, was admitted to the Hospital because of a four-day history suggestive of intestinal obstruction. At exploration a pelvic abscess was found and drained but no obstructive lesion was discovered. Postoperatively he was started on gastric suction and was given sulfadiazine, sodium lactate and penicillin. The patient did well for a few days postoperatively when he became disorientated, uncooperative and violently belligerent. He fought with his attendants, repeatedly climbed out of bed, broke restraints and attempted to pull out the gastric suction and infusion tubes. During two days of this behavior the carbon dioxide combining power was reported as "over 100" and his blood chloride fell to 334 mg. Chvostek and Trousseau signs were positive and the blood calcium fell to 8.1 mg. An electrocardiogram showed typical features of hypocalcemia. He was given 40 Gm. of ammonium chloride parenterally during the day and night, and on the following day there was complete clearing of the disorientation and the patient became mild and cooperative. It is noteworthy that throughout his alkalosis the blood urea nitrogen did not rise above normal and the urine was normal during the episode.

Case vii. E. P., a fifty-three year old markedly emphysematous man, was admitted to the Hospital for a perforated peptic ulcer. Postoperatively he was placed on gastric suction, given intravenous sulfadiazine and sodium lactate and at first did well. On the ninth postoperative day, however, he was slightly disorientated and did not recognize his relatives. On

the following day he was found in a state of confusion with a pronounced word aphasia. Three hours later he became semiconscious, would not respond to his name and resisted examination. The respirations were slow and shallow and he was cyanotic. There were numerous muscular twitchings and the extremities were spastic. At this time the carbon dioxide combining power was reported as "over 90" and the blood chlorides were 246 mg. (42 mEq.). He was given 20 Gm. of ammonium chloride by gavage in 1,000 cc. of water. At the end of this time his mental state had improved so that he was able to identify himself, name objects and respond to commands. The carbon dioxide was again reported as over 90 volumes per cent and he was given another 20 Gm. of ammonium chloride by gavage. At the completion of this treatment the carbon dioxide combining power was reported as 59 volumes per cent, the chlorides were 485 mg. and the patient was well orientated and cooperative. The blood urea nitrogen remained normal throughout.

CASE VIII. H. H., a fifty-six year old white man, was admitted to the Hospital for symptomatic treatment of intractable pain from a peptic ulcer. The general physical examination was essentially negative except for emphysema. He was given a diet of milk, cream and alkali powders. On this regimen he did well and the pain gradually abated. On the twelfth hospital day, however, he began to complain of headache, drowsiness and generalized weakness. He was noted to be apathetic and, although previously active, chose to remain in bed all day. During the next few days the drowsiness continued; he was disgusted with his milk feedings. He became restless, vomited more frequently and exhibited muscular twitching. The urine, which was normal on admission, for twelve days during the period of alkalosis showed albumin, microscopic hematuria and hyaline and granular casts. After this period it was normal.

CASE IX. D. O., a seventeen year old white boy, was admitted to the Hospital because of vomiting from peptic ulcer. During the height of one of the obstructive periods the carbon dioxide combining power rose to "over 90" and the blood urea nitrogen to 36 mg. Carpopedal spasm was noted during this episode. Following gastroenterostomy his blood chemical findings returned to normal. Throughout all of the hospital course, however, there was never any disturbance of the sensorium and the urine remained normal throughout. Unfortunately, there has been no determination of renal function since his discharge from the hospital.

COMMENTS

Eight of the nine patients were seen in consultation on the surgical service. Primary conditions included one subtotal pancreatectomy designed to correct hypoglycemia, two patients with intestinal obstruction, one patient with pelvic abscess simulating intestinal obstruction, one with cancer of the colon without obstruction and four patients with peptic ulcers. Three of the patients with peptic ulcer were also emphysematous. The cause of the alkalosis could be attributed in six of the nine patients to the simultaneous use of gastric lavage and the liberal use of sodium lactate with or without sulfadiazine. In two of the emphysematous patients with peptic ulcer, the administration of Sippy powders or similar alkaline treatment seemed to be the exciting cause. In one patient without emphysema, alkalosis appeared to be attributable to continued vomiting.

Both mental disturbance and renal insufficiency were apparent in six of the nine patients. Two showed delirium only, and one developed renal insufficiency without mental disturbance. During the alkalosis respiration became shallow and slow and in some instances so inefficient as to result in cyanosis. Muscular twitching and spasticity were observed in one patient. In another, there were carpopedal spasms, while in still another patient there was a severe generalized epileptiform seizure of several minutes' duration. It was notable, however, that in only one patient could the Chvostek or Trousseau signs be elicited. The highest recorded carbon dioxide combining power was 110 volumes per cent, although in a

number of patients the value was reported approximately as "over 90" or "over 100" volumes per cent. Definite lowering of chloride values accompanied the increases in bicarbonate. In one instance the very low value of 246 mg. per cent was found. The urinary picture varied. In three patients no abnormalities were found during the episode of alkalosis. All of the other patients showed slight or moderate albuminuria. Hyaline and granular casts appeared frequently and in one patient microscopic hematuria was evident. Blood urea nitrogen was elevated and in three patients attained levels of over 70 mg. per cent.

Much more impressive than these signs, however, were the changes which took place in the sensorium. Usually the first abnormality to be noted was a slight change in the personality. Patients who were previously cooperative and placid became irritable, exaggerated their complaints, sought extra attention or were excessively demanding. One man who was on a regimen of alkaline powders for peptic ulcer lost his taste for milk and complained of nausea. Several suffered from a dull, aching headache of muscle spasm type. In one instance, it resembled vascular headache with throbbing pain of high intensity and hemicrania. Vomiting was observed and in one patient was frequent and violent. Generalized weakness was apparent but at times was accompanied by muscular twitching and hyperreflexia. Activity was lessened, mentality appeared to be dulled and drowsiness, apathy or lethargy developed. Accompanying these manifestations there was disorientation in time and place, often with belligerent uncooperativeness. Eight of our patients at one stage became completely disorientated with marked changes in personality. One struck a nurse and a doctor. Others tore out venoclysis needles or gastric suction tubes. Some tried to climb out of bed dragging infusion apparatus with them. When the state of alkalosis was allowed to continue, evidence of profound derangement of function of the nervous system became manifest. One of our patients had a severe generalized convulsion, another developed anomia.

In presenting the record of these cases there can be no claim of discovery or originality. It has long been known that alkalosis may result either from the loss of large amounts of the acid secretion of the stomach, or from the ingestion of excess amounts of alkaline medication.[2,3] Since 1915, when Sippy introduced the use of alkaline powders for the treatment of peptic ulcer, it has been realized that not all patients are able to tolerate them and that 5 to 10 per cent of them will develop considerable degrees of alkalosis.[2] As long ago as 1923, Hardt and Rivers[3] in their excellent study of the basis of symptoms in alkalosis, reported that their patients were irritable and introspective, complained of headache, nausea, vomiting and weakness, that their respirations were slow and that they were prostrated and drowsy. They also found that the urine of such patients might, during alkalosis, show albumin, red blood cells and casts which would disappear with the return of the carbon dioxide combining power to normal levels. Later studies by many observers have revealed evidence of serious renal derangement or of actual nephritis developing during periods of alkalosis and persisting for variable intervals following cessation of the alkalotic state.[3–9]

There are, however, a number of circumstances connected with our observations that seem to deserve some emphasis. A great majority of previous studies have been concerned with alkalosis developing in patients with peptic ulcers who were treated with alkaline powders, and severe vomiting which accompanies gastric conditions and intestinal obstruction resulted. In six of our patients, on the other hand, symptoms appeared to develop as a result of a com-

bination of gastric suction and the administration of sodium lactate, both measures which at present have great vogue and a high measure of utility in post-operative conditions.

The danger of removal from the body of large amounts of acid secretion is not always kept in mind, nor is it always realized that the very useful sodium lactate solution may add greatly to the store of sodium bicarbonate unless corrected by the simultaneous administration of sodium chloride. It is worthy of note that at the time these patients were seen in consultation there was no realization of their true state on the part of those who had attended them. To them it was disturbing indeed to witness in the course of a previously satisfactory postoperative convalescence, the development of disgust for food, nausea, vomiting or irritability and disorientation with subsequent apathy, lethargy, stupor or spasticity, twitching and even convulsive seizures. When these symptoms were combined with increasingly abnormal urinary findings and an alarming retention of non-protein nitrogen, there was much cause for confusion in diagnosis unless one were aware of all the consequences of the alkalotic state.

Another aspect which deserves inquiry is the persistence of renal damage arising from the continuance of alkalosis. From our own observations and from many more in the literature there is reason to believe that recovery of normal renal function may be long delayed and that pathologic changes may persist even in patients who have previously exhibited no signs of kidney disease.[5,8,9,10] One of our patients showed retention of non-protein nitrogen twelve months after the alkalotic episode. In the literature similar observations are numerous[5,6,7,11] and in the case of Brown and Eusterman[12] impaired renal function was demonstrable even after six years. Such records lead to a disturbing fear that alkalosis may not be an entirely temporary and trivial phenomenon and indicate that the prevention or prompt correction of the condition may be of considerable importance to the subsequent health of the individual.

Still another circumstance in our observations may deserve passing comment. In three of the four patients who developed alkalosis during the treatment of peptic ulcer with alkaline powders, there was a preexisting emphysema. It seems possible that the tendency to elevated bicarbonate which develops in emphysematous patients may render them more than ordinarily susceptible to the consequences of alkalosis when they are given alkaline therapy.[13,14]

In the management of alkalosis it is important to realize that the situation will correct itself rather promptly if the cause can be removed. In several of our patients spontaneous remission occurred when the alkaline powders were withdrawn or the gastric suction and parenteral administration of lactate solution were discontinued. In others, however, it appeared necessary or very desirable to obtain prompt effects. To accomplish this ammonium chloride was given parenterally by the method of Zintel, Rhoads and Ravdin.[15] Briefly, the method consists of the intravenous administration of autoclaved 2 per cent solution of ammonium chloride in distilled water. The usual procedure was to administer a liter of such a solution (20 Gm. ammonium chloride) over a period of two and one-half to three hours. The results were satisfactory and frequently dramatic, with almost immediate improvement in the orientation and cooperation of the patient as well as rapid disappearance of the disturbing symptoms.

SUMMARY AND CONCLUSIONS

1. The current use of gastric suction and sodium lactate solutions may lead to a condition of alkalosis which may be accompanied by changes in personality, delirium,

stupor or convulsions and by renal insufficiency which tends to persist.

2. The state is often unrecognized and if neglected may lead to serious consequences.

3. Removal of the causes of the alkalosis will lead to gradual or fairly prompt recovery of the abnormal mental state. A more rapid correction may be accomplished by the parenteral administration of ammonium chloride.

4. It is possible that emphysematous patients are more than ordinarily susceptible to alkaline therapy.

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Electrolyte Partition in Patients with Edema of Various Origins*

Sodium and Chloride

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THE orthodox concept of edema as a physicochemical phenomenon involving the extravasation, primarily of saline solution, over the peripheral capillary barrier between blood stream and extracellular tissue fluid has been challenged in recent years by numerous observers. The postulated normal equilibrium between hydrostatic pressure outward and oncotic pressure inward has been a serviceable hypothesis since most medical entities have been associated with a disturbance of one or the other of these vectors. Thus, the teaching that "in cardiac decompensation stasis causing increased hydrostatic pressure in the capillary bed is apparently the important factor in causing edema" † has long been standard. Increased hydrostatic pressure in the capillary was plausible enough in view of the demonstrable increase in venous pressure characteristic of heart failure. Similarly, other disease processes, notably cirrhosis and nephrosis, in which fluid retention is present have been characterized by the reduction of some constituent of the blood, chiefly albumin, to which could be attributed a diminution of oncotic pressure and hence the production of edema.

Discrepancies in this system have been pointed out, both in heart failure and in the hypoproteinemic states, but the attention of research workers and clinicians alike has remained, for the most part, directed toward events taking place at the capillary membrane. That the kidneys participate actively in the "retention of salt and water" was, however, at least strongly implied by Schroeder and Futcher in 1942.[1] These workers studied a group of five cardiac patients and two controls and found that doses of salt and water were imperfectly excreted by the experimental group as compared with the two normal subjects. They found, in addition, that the urea clearance capacity of the cardiacs was not diminished and that mercurial diuretics promoted the output of salt and water. Their studies brought out three questions: first, was the decreased excretion of salt and water due to decreased renal filtration rate; second, were circulatory changes demonstrable in the kidneys and third, was tubular behavior due to the influence of a hormone? This viewpoint was supported in 1944 by Warren and Stead[2] who formulated the events of edema formation in cardiac failure as prefaced by impaired cardiac function which by unknown mechanisms led to decreased renal excretion of sodium and water and, thereby, to increased blood volume and elevated venous pressure.

Our own experience[3] with a massively decompensated patient upon whom repeated clearance determinations of inulin, diodrast, chloride, phosphate and sodium were performed, indicated that profound disturbances of renal physiology were reflected,

† Peters and Van Slyke. Williams & Wilkens, Baltimore, 1932.

* From the Department of Medicine, Northwestern University Medical School, Chicago, Ill. Funds were furnished by the U. S. Public Health Service, Research Division.

not in a reduction of working nephrons and hence diminution of filtration rate, but in an altered manner or pattern of tubular reabsorption of sodium and chloride. Thus, the acute fluid retention and oliguria of severe decompensation could not be correlated with a failure on the part of the glomeruli to filter but rather with a sharp increase in the tubular reabsorption of water and sodium and a variable behavior toward chloride. A recent paper of Reaser and Burch[4] reports a retention of sodium in cardiac decompensation, demonstrated by the use of radioactive sodium, a finding which contributes to the concept that the conversion of fluid equilibrium into positive fluid balance is not accomplished without tubular intervention.

The validity of hypoproteinemia as a cause of hepatic cirrhosis, on the other hand, has also been questioned. Absence of agreement on the part of students working with inert membranes as to the critical concentration of albumin in the maintenance of fluid equilibrium has been striking and in 1945 Ralli and co-workers[5] reported no correlation between plasma albumin and the presence of ascites. They went on to show that an antidiuretic hormone was present in augmented concentration in the urine of patients with ascites and postulated that the liver normally inactivates the antidiuretic hormone.

The present study was undertaken for the purpose of defining more specifically the renal aspects of water and electrolyte balance in congestive heart failure.

Methods. Sodium and chloride clearances were determined in a group of cardiacs who gave evidence of fluid retention. No attempt was made to classify the etiological factor.

The first group of controls consisted of normal individuals. The second group was intended to consist of patients suffering from edema of other than cardiac origin. The findings in the latter group, however, broke down into patterns which evidently represented characteristics of the two other types of edema studied, namely, hepatic cirrhosis and the nephrotic syndrome. The problem was, therefore, reorganized as a study of the sodium-chloride ratio in (1) congestive heart failure, (2) hepatic cirrhosis and (3) nephrosis.

The data were found to be more significant when considered in terms of milliequivalents of urine sodium and chloride undiluted by the relatively unvarying plasma concentration; the study was continued on single morning urine specimens. Since conclusions based upon single specimens alone might be considered unreliable, several twenty-four-hour outputs have been added.

All cardiac patients with edema had been on low sodium diets for variable periods and all were taking ammonium chloride. Most cirrhosis patients were on normal salt intakes; a few received ammonium chloride as did several of the nephrosis cases. For the purpose of evaluating a diuretic management under the conditions of the present study four normal individuals were included before and after a period of three to fifteen days on a similar regimen.

Nine patients giving evidence of water retention as a result of various kinds of heart failure were studied by means of sodium and chloride clearances. The tests were performed in the morning in the fasting state. The patients were permitted to drink water as they chose. The control series consisted of thirteen subjects who were free of heart disease or of edema on any other basis. Two clearance periods of two hours each were determined, the blood specimen being drawn at the end of the first period and immediately centrifuged. The continuation studies included urine samples on twenty-two cardiacs, twenty-one normal subjects, eighteen patients with hepatic cirrhosis and eight with nephrosis.

The sodium ion concentration in urine and serum filtrate was determined nephelometrically after precipitation as sodium magnesium uranyl acetate, according to a modification of the method of Lindsay and his co-workers.[6] The readings were made by means of a two-cell photoelectric nephelometer with a reproducible accuracy of

3 per cent. The chloride determinations were made by titration with mercuric ion, using s-diphenyl-carbazone as an indicator.[7] This method was found to be comparable in accuracy to that of Whitehorn or Volhard.

Determinations on twenty-four-hour collections employed the standard method of Volhard for chloride and colorimetric readings of the uranyl acetate precipitate for sodium.

TABLE I

CARDIAC DECOMPENSATION

Patient	Sodium Clearance	Chloride Clearance	Clearance Ratio	mEq./L. Sodium	mEq./L. Chloride	mEq. Ratio
1	0.07	0.65	0.10	9	82	0.11
2	0.18	1.38	0.15	5	49	0.10
3	0.10	0.24	0.44	31	56	0.55
4	0.27	1.1	0.24	36	107	0.30
5	0.64	1.5	0.42	116	180	0.64
6	0.21	0.43	0.49	67	100	0.67
7	0.52	1.4	0.37	30	60	0.50
8	0.02	0.17	0.11	2	15	0.13
9	0.06	0.13	0.48	17	31	0.55
10				42	77	0.55
11				3	10	0.30
12				28	85	0.33
13				75	110	0.68
14				73	155	0.47
15				10	15	0.67
16				11	31	0.35
17				66	125	0.53
18				4	13	0.31
19				33	86	0.38
20				1	10	0.10
21*				5	34	0.13
22*				2	52	0.04
			Average 0.32			Average 0.40
NORMAL						
1	0.41	0.65	0.63	120	140	0.86
2	0.77	1.3	0.59	96	107	0.90
3	0.83	1.2	0.69	110	120	0.92
4	0.56	0.77	0.73	97	99	0.98
5	0.50	0.83	0.60	29	33	0.88
6	0.83	1.4	0.59	74	90	0.82
7	0.66	1.1	0.60	150	180	0.83
8	0.96	1.7	0.56	140	180	0.78
9	0.87	1.3	0.67	210	230	0.91
10	0.88	1.3	0.68	160	170	0.94
11	0.84	1.5	0.56	140	180	0.78
12	0.93	1.3	0.72	100	100	1.00
13	0.76	1.2	0.63	130	140	0.93
14				198	197	1.00
15				100	170	0.94
16				230	260	0.89
17				140	135	1.04
18				130	140	0.93
19				140	170	0.82
20				180	200	0.90
21*				37	46	0.81
			Average 0.63			Average 0.90

* Twenty-four-hour specimens quoted in milliequivalents per twenty-four hours.

Results. Table I shows the clearance studies. The average ratio of sodium to chloride clearance in the cardiac group was found to be 0.32, with a range of 0.10 to 0.49. The control subjects gave an average ratio of 0.63, with a range of 0.56 to 0.73.

TABLE II

Normal Regimen					Low Salt, Acid Ash Diet, Ammonium chloride 4 Gm. Daily		
Patient	mEq./L. Sodium	mEq./L. Chloride	Sodium / Chloride	Days	mEq./L. Sodium	mEq./L. Chloride	Sodium / Chloride
1	106	106	1.00	4	58	80	0.72
2	146	202	0.73	3	81	86	0.94
3	113	113	1.00	8	61	67	0.91
4	45	48	0.94	14	43	43	1.00
			Average 0.92				Average 0.89
Cirrhosis					Nephrosis		
1	*	79			26	31	0.84
2	*	43			19	26	0.73
3	*	32			65	72	0.90
4	14	41	0.34		70	67	1.04
5	23	80	0.29		82	77	1.07
6	*	63			73	85	0.86
7	*	39			80	72	1.11
8	9	60	0.15		65	79	0.82
9	19	80	0.24				
10	52	110	0.47				
11	59	132	0.45				
12	9	55	0.16				
13	2	60	0.03				
14	19	75	0.25				
15	2	15	0.13				
16	4	31	0.13				
17	5	86	0.06				
18	45	77	0.58				
19	30	133	0.23				
			Average 0.25				Average 0.92

* Below 2.

The continuation studies are presented in Tables I and II. The cardiac patients showed a sodium-chloride ratio, in milliequivalents, of 0.10 to 0.67, with an average of 0.40 compared with a control average of 0.90. Four normal subjects averaged 0.92 without salt restriction and 0.89 after a period of salt restriction and medication of ammonium chloride, 4 Gm. daily.

Sodium was markedly reduced in the cirrhosis group. Chloride excretion was also depressed but the average sodium-chloride ratio was considerably below that found in the cardiac group.

The nephrotic syndrome, on the other hand, showed a normal sodium-chloride partition.

COMMENTS

Assuming that sodium is as freely filterable in the extrarenal pathological states under discussion as in the normal conditions upon which present concepts of renal dynamics were established, the tubules are seen in these studies to exercise definite selectivity in the reabsorption of certain electrolytes. Whatever may be the exchange at the capillary membrane, the activity of the renal tubules is clear. We are dealing then with conditions in the kidneys which are mediated by the blood stream and are somehow correlated with an increase in the volume of extracellular tissue fluid and hence an increase in the total body sodium. It is evident that the augmented extracellular fluid compartment could only affect the kidneys by means of the blood stream but, since the blood concentrations of electrolytes are known to be normal, such a mechanism would be difficult to conceive. If, on the other hand, some other factor capable of modifying tubular reabsorption of sodium and chloride could be stimulated by changes in the composition of extracellular tissue fluid, those changes would be likely to include alterations in the sodium or chloride concentrations. The composition of ascitic and edema fluid have been found, however, to show no such alterations; so although it is possible that some other change in the extracellular tissue fluid could initiate a process which could in turn act on the renal tubules, it seems rather more probable that the altered reabsorptive faculties of the tubules precedes the extravasation phenomenon at the capillary membrane. The results shown here, as well as the conjectures which they stimulate, are compatible with the postulates of Warren and Stead.[2]

Considering now the case of cirrhosis with fluid retention, the almost total absence of sodium in the urine is difficult to reconcile with the orthodox view of fluid storage on the basis of hypoproteinemia, portal obstruction or increased intra-abdominal pressure. The present study shows a relative and an absolute decrease in sodium excretion but, since the data do not include a time element, the retention of water and the increased excretion of chloride characteristic of the pitressin action suggested by the New York group[5] cannot be demonstrated. It is clear, however, that the renal tubules are playing a rôle which earlier theories failed to consider and it is probable that they are responding to a factor which may be primarily hormonal or chemical.

In contrast with the electrolyte pattern of hepatic cirrhosis and of cardiac decompensation, the nephrotic syndrome showed no deviation from normal in the sodium-chloride ratio. This finding is striking, since cirrhosis and nephrosis have the common factor of hypoproteinemia and might, therefore, have been expected to show a similar urine electrolyte pattern.

CONCLUSIONS

The formation of edema in cardiac decompensation and in hepatic cirrhosis is associated with a decrease in the ratio of urine sodium to chloride in terms of milliequivalents.

The edema of nephrosis cannot be identified with any alteration in the urine sodium-chloride ratio. The demonstration of specific and characteristic electrolyte patterns in edema of various origins suggests that the kidney plays an active rôle in the establishment and maintenance of certain types of fluid retention.

SUMMARY

Data have been collected on electrolyte partitions in urine of patients with (1) congestive heart failure, (2) hepatic cirrhosis and (3) nephrosis, for the purpose of demonstrating renal function in fluid retention associated with these entities.

Clearance evaluation of sodium and chloride in cardiac decompensation and in normal subjects showed a decrease in sodium clearance with respect to chloride

in the cardiac group. Comparison of sodium to chloride in milliequivalent ratios showed a constant decrease in sodium excretion and a depression in the sodium-chloride ratio. This depression varied directly with the severity of the disease process and the degree of fluid retention. These findings are compatible with the hypothesis that edema is a result of retention of sodium by the renal tubules rather than of increased venous pressure.

Patients with hepatic cirrhosis were found to release greatly reduced amounts of sodium; several showed only traces. In this group, the sodium-chloride ratio was even more sharply reduced than in the cardiac group. Such evidence of pathological physiology in the kidney is difficult to reconcile with the widely held theory that fluid retention in cirrhosis is inversely proportional to the plasma albumin concentration.

No disturbance in the normal sodium-chloride ratio could be found in nine patients with nephrosis.

It was concluded that fluid retention in cardiac decompensation and in hepatic cirrhosis is not due solely to increased hydrostatic and decreased oncotic pressure, respectively, but to disturbances of electrolyte metabolism intimately associated with the renal tubules.

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Serum Concentrations of Penicillin G in Man Following Intramuscular Injection in Aqueous Solution and in Peanut Oil-Beeswax Suspension*

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THE therapeutic action of penicillin probably rests to a large extent on its direct bactericidal action. In order to kill the largest number of organisms in the shortest possible time it is therefore necessary to provide at the focus of infection a concentration which is maximally effective for the particular organism. This tissue concentration of penicillin is obviously not susceptible of direct measurement. The serum concentration of penicillin can, however, be determined; and although such factors as the binding of penicillin by serum proteins,[1] its varying rate of diffusion out of the blood into the several tissues and its binding or destruction in the tissues,[2,3] enjoin caution in the interpretation of the blood level data, these do provide information as to the concentration of penicillin available for distribution at any one moment.

It is therefore of some therapeutic interest to know the average serum concentration provided by a given dose of penicillin at varying periods after its administration. With that information, one can estimate how often a given dose of penicillin should be repeated in order to maintain at the focus of infection a concentration effectively bactericidal for the particular organism. The available data with respect to the serum concentrations of penicillin in man[4–9] deal largely with amorphous preparations containing several penicillin species in unknown proportions.[10] The data herein reported are based entirely on preparations of crystalline sodium penicillin G.

MATERIALS AND METHODS

One hundred thirty-eight patients from the Johns Hopkins Hospital were used in this study; 110 were in-patients and 28 were undergoing ambulatory treatment for gonorrheal infections. Eighty-three were males. The study was limited to patients who had received no penicillin during the forty-eight hours preceding the test and whose renal and cardiac functions were essentially normal. No limitations were placed on fluid intake or on the degree of physical activity.

For injection in aqueous solution two lots of crystalline penicillin G from two different manufacturers were employed. One was a commercial lot and the other was a highly purified sample prepared for experimental use. The results with the two lots did not differ demonstrably and they are not distinguished in the tables. For administration a 6 per cent solution (60 mg. per cc., equivalent to 100,000 Oxford units) was prepared. The volume injected was then adjusted to the body weight to give

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dosages of 10, 3, 1.5, 0.6, 0.3, or 0.15 mg./Kg. (total dosages of 1,200,000 units down to 18,000 units in a man weighing 72 Kg. or approximately 160 pounds). The largest single injection was 12.0 cc. (1,200,000 units) and the smallest was 0.11 cc. (11,000 units). The outer upper quadrant of the buttock was the site of injection; the plunger was withdrawn prior to injection in order to avoid intravenous administration. All tests were begun at approximately 9 A.M. and blood samples were taken by venipuncture at appropriate intervals.

Four lots of crystalline penicillin G suspended in peanut oil and beeswax from two different manufacturers were used in the experiments with that preparation. All contained 180 mg. (300,000 units) per cc. Following preliminary warming in a water bath at 40 to 50°C., the material was withdrawn into an unheated, dry-sterilized syringe of appropriate capacity. In making the injection, a dry 20-gauge needle was first inserted into the gluteal muscles. If no blood appeared within a few seconds, the syringe containing the suspension was attached and the operation completed. Tests were begun at either 9 A.M. or 9 P.M. No embolic or allergic phenomena were noted and the transitory, local discomfort was readily explained on the basis of the volume of material injected. The largest dose employed was 4.0 cc., equivalent to 1,200,000 units and the smallest was 0.35 cc. (105,000 units).

The sera were assayed by a modified Kirby-Rantz method involving the use of serial dilutions of serum, and in which inhibition of hemolysis by the C-203 strain of Streptococcus pyogenes was the end point.[11] All the assays were corrected for the inhibitory effect of human serum on penicillin activity *in vitro*,[1,11–13] using the corrective factors determined by one of us for this particular assay method.[14] The serum concentrations are expressed in the figures and tables as both micrograms and units of penicillin G per cc. of serum, 1 microgram being equivalent to 1.67 Oxford units.

BLOOD LEVELS AFFORDED BY PENICILLIN G IN AQUEOUS SOLUTION

In Table I are shown the median serum concentrations observed one-half, one, two, four and eight hours after the injection of penicillin G in aqueous solution. The data are presented graphically. (Fig. 1.) Every value in either Table I or Figure 1 is based on a minimum of ten subjects injected at each dosage level and tested at each time period. Table IA gives the range of variation in the individual subjects, the standard deviation from the median and the standard error of the median for each dosage level and at each time period tested.

The regularity of the serum penicillin curves is apparent in Figure 1. At low dosages the serum concentration was almost linearly related to the amount of penicillin injected. Thus, one hour after dosages of 0.15, 0.3, 0.6, 1.5, 3 and 10 mg./Kg., the blood levels were 0.095, 0.17, 0.38, 1.1, 3.5 and 11.3 micrograms per cc. respectively. At all dosages the serum concentrations fell off at the same initial rate of approximately 70 per cent per hour[15] (i.e., 70 per cent of the residual penicillin disappeared each succeeding hour). After the first few hours, however, the serum concentrations fell off more slowly. This is evident in the curves obtained in patients who had received large doses of penicillin (top curves of Fig. 1) and may perhaps be related to the fact that at these high dosages a significant reservoir of penicillin is established in the tissues soon after its injection. When, because of the rapid urinary excretion, the plasma concentration of diffusable penicillin falls below that in the tissues, the direction of flow is probably reversed. The diffusion of penicillin out of the tissues into the blood may then serve to maintain the plasma concentration at significantly higher levels than would otherwise have been the case.[12,14,16]

Whatever the explanation, it is evident in Figure 1 that after large doses of penicillin the serum concentration is regularly higher than one would anticipate from the dif-

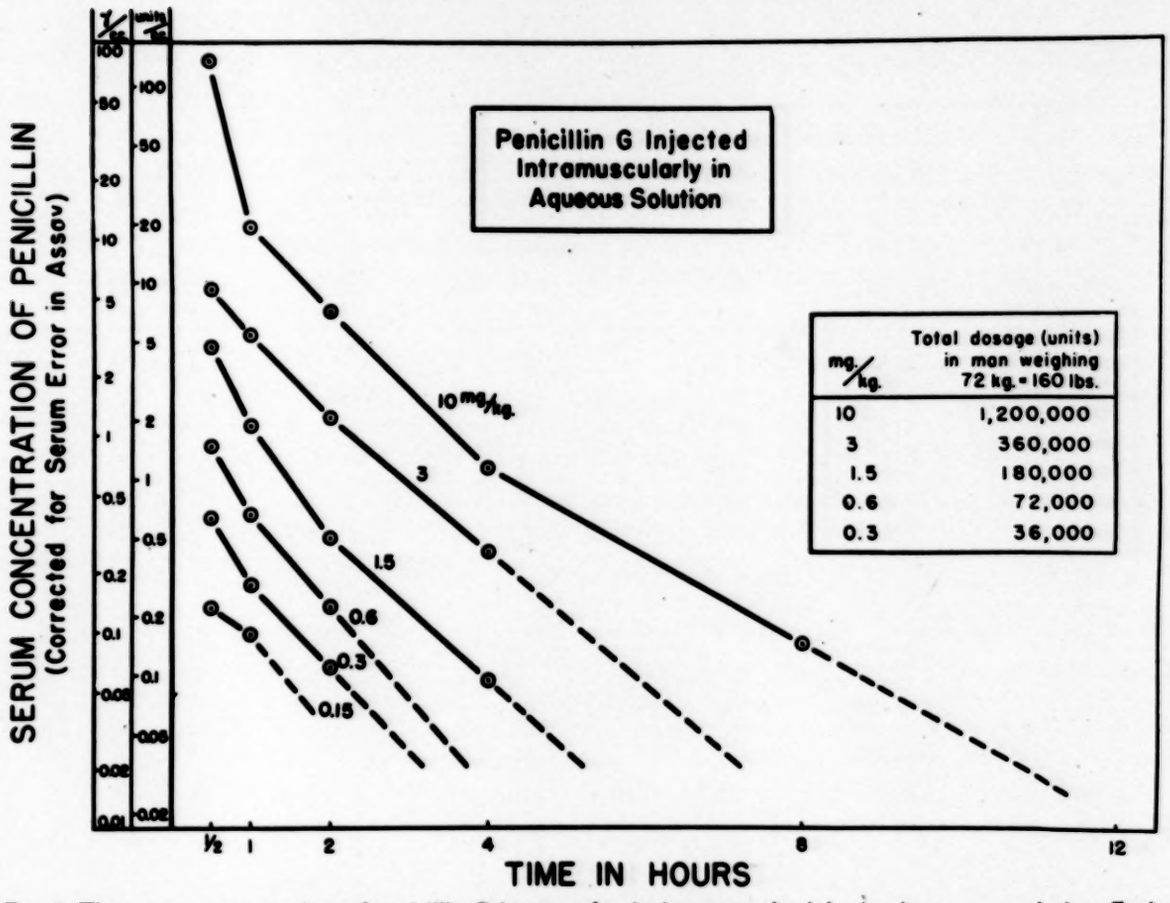


FIG. 1. The serum concentrations of penicillin G in man after its intramuscular injection in aqueous solution. Each value in the figure is the median of at least ten patients, as indicated in Table IA.

TABLE 1

SERUM LEVELS OF PENICILLIN G FOLLOWING INTRAMUSCULAR ADMINISTRATION IN AQUEOUS SOLUTION

Dosage, Mg./Kg.	No. Patients Tested	Total Dose in Man Weighing 72 Kg. (160 lbs.)		Time in Hours after Single Injection					Time in Hours after Single Injection				
				½	1	2	4	8	½	1	2	4	8
		Mg.	Units	Serum Concentrations in Micrograms per cc. (Median)					Serum Concentrations in Units per cc. (Median)				
10.00	10	720	1,200,000	17.9	11.3	4.4	0.67	0.085	29.9	18.9	7.3	1.1	0.14
3.0	10	216	360,000	5.6	3.5	1.2	0.25	<0.015	9.4	5.9	2.1	0.42	
1.5	16	108	180,000	2.8	1.1	0.3	0.055	<0.015	4.7	1.8	0.5	0.092	
0.6	16	43	72,000	0.87	0.38	0.13	<0.015	.....	1.5	0.63	0.21		
0.3	10	22	36,000	0.37	0.17	0.065	<0.015	.....	0.62	0.28	0.11		
0.15	10	11	18,000	0.13	0.095	<0.015	.....	.....	0.22	0.16			

TABLE 1A

DEGREE OF VARIATION FROM PATIENT TO PATIENT IN THE SERUM CONCENTRATION OF PENICILLIN G FOLLOWING INTRAMUSCULAR INJECTION IN AQUEOUS SOLUTION

Dosage, Mg./Kg.	No. Patients		Time in Hours					
			½	1	2	4	8	12
			Serum Concentrations in Micrograms per cc.					
10	10	Median	17.9	11.3	4.35	0.67	0.085	<0.015
		Range High	21.2	17.6	6.4	1.33	0.21	
		Range Low	11.1	6.0	1.67	0.21	<0.015	
		σ Med.	3.63	3.42	2.02	0.41	0.068	
		Standard Error	0.79	0.77	0.46	0.09	0.017	
3	10	Median	5.55	3.5	1.23	0.25		
		Range High	12.0	5.5	4.0	0.83		
		Range Low	3.75	1.8	0.3	0.1		
		σ Med.	2.48	1.31	0.56	0.21		
		Standard Error	0.58	0.29	0.23	0.05		
1.5	16	Median	2.8	1.1	0.3	0.055		
		Range High	9.6	3.2	0.65	0.13		
		Range Low	1.6	0.66	0.16	>0.015		
		σ Med.	2.1	0.87	0.16	0.039		
		Standard Error	0.41	0.17	0.032	0.01		
0.6	16	Median	0.87	0.38	0.13			
		Range High	1.4	0.62	0.2			
		Range Low	0.33	0.15	0.081			
		σ Med.	0.34	0.17	0.036			
		Standard Error	0.071	0.036	0.006			
0.3	10	Median	0.37	0.17	0.065			
		Range High	0.41	0.29	0.065			
		Range Low	0.25	0.11	<0.011			
		σ Med.	0.044	0.08	0.045			
		Standard Error	0.01	0.018	0.013			
0.15	10	Median	0.13	0.095				
		Range High	0.27	0.12				
		Range Low	0.1	0.05				
		σ Med.	0.065	0.063				
		Standard Error	0.02	0.017				

σ Med. = Standard deviation of median.

TABLE II

SERUM LEVELS OF PENICILLIN G FOLLOWING INTRAMUSCULAR ADMINISTRATION OF SUSPENSIONS IN PEANUT OIL AND BEESWAX

(LOTS A, B AND C RAPIDLY ABSORBED)

Dosage, Mg./Kg.	No. Patients Tested	Total Dose in Man Weighing 72 Kg. (160 lbs.)		Time in Hours after Single Injection							Time in Hours after Single Injection						
				½	1	2	4	8	12	24	½	1	2	4	8	12	24
		Mg.	Units	Serum Concentrations in Micrograms per cc. (Median)							Serum Concentrations in Units per cc. (Median)						
10.0	9	720	1,200,000	2.0	4.0	6.0	5.23	2.4	0.98	0.098	3.4	6.66	10.0	8.70	4.0	1.62	0.16
3.0	13	216	360,000	0.5	0.6	0.89	0.87	0.4	0.28	0.085	0.84	1.0	1.5	1.4	0.67	0.47	0.14
1.5	12	108	180,000	0.45	0.47	0.53	0.33	0.26	0.12	<0.015	0.75	0.78	0.88	0.55	0.43	0.2	

TABLE IIA

DEGREE OF VARIATION FROM PATIENT TO PATIENT IN SERUM CONCENTRATION OF PENICILLIN G FOLLOWING ADMINISTRATION IN PEANUT OIL-BEESWAX SUSPENSION (LOTS A, B AND C RAPIDLY ABSORBED)

Dosage, Mg./Kg.	No. Patients		Time in Hours						
			½	1	2	4	8	12	24
			Serum Concentrations in Micrograms per cc.						
10	9	Median	2.0	4.0	6.0	5.23	2.4	0.98	0.098
		Range High	6.7	6.7	8.8	10.0	4.8	2.5	0.19
		Range Low	1.4	2.4	3.0	2.5	0.3	0.045	<0.015
		σ Med.	1.87	1.21	1.61	2.17	1.25	0.81	0.058
		Standard Error	0.5	0.29	0.38	0.54	0.34	0.19	0.015
3	13	Median	0.5	0.6	0.9	0.87	0.4	0.28	0.085
		Range High	0.62	1.0	1.25	1.6	0.91	1.04	0.16
		Range Low	0.28	0.31	0.12	0.26	0.13	<0.015	<0.015
		σ Med.	0.11	0.27	0.13	0.36	0.26	0.3	0.035
		Standard Error	0.025	0.06	0.07	0.081	0.057	0.067	0.009
1.5	12	Median	0.45	0.47	0.53	0.33	0.26	0.12	<0.015
		Range High	0.63	1.6	2.0	2.2	0.75	0.21	
		Range Low	0.015	<0.015	<0.015	0.128	<0.015	<0.015	
		σ Med.	0.26	0.5	0.75	0.62	0.21	0.055	
		Standard Error	0.045	0.011	0.16	0.13	0.057	0.22	

ference in dosage, assuming a linear relationship. It is pertinent to note that, in general, it required a 2.5- to 10-fold increase in the dosage of penicillin in order to prolong a given plasma level by one hour. This merely reflects the rapid excretion of the drug. An increase in the dosage per injection is obviously a wasteful method of prolonging the time of action of penicillin; but in the sick patient, it is perhaps preferable to the administration of repeated small injections. The choice between (1) a small number of relatively large injections, (2) a large number of small injections and (3) a suspension of penicillin in oil and beeswax involves a number of factors (e.g., cost of penicillin, cost of hospitalization, physical condition of the patient, desirability of ambulatory treatment, etc.). The discussion of these factors is not within the scope of this paper.[13,14]

BLOOD LEVELS AFFORDED BY PENICILLIN G IN PEANUT OIL-BEESWAX SUSPENSION

The median serum levels of penicillin following the administration of penicillin G in peanut oil-beeswax (pooled data for three of the four lots tested) are given in Table II, Table IIA and Figure 2. As has been found by numerous previous workers, the highest serum level was not attained for several hours after administration and the peak concentrations were lower than after a corresponding dose of the aqueous product. The slower absorption of penicillin was further reflected in the slow rate of fall of the serum concentration and in the long period of time for which penicillin remained

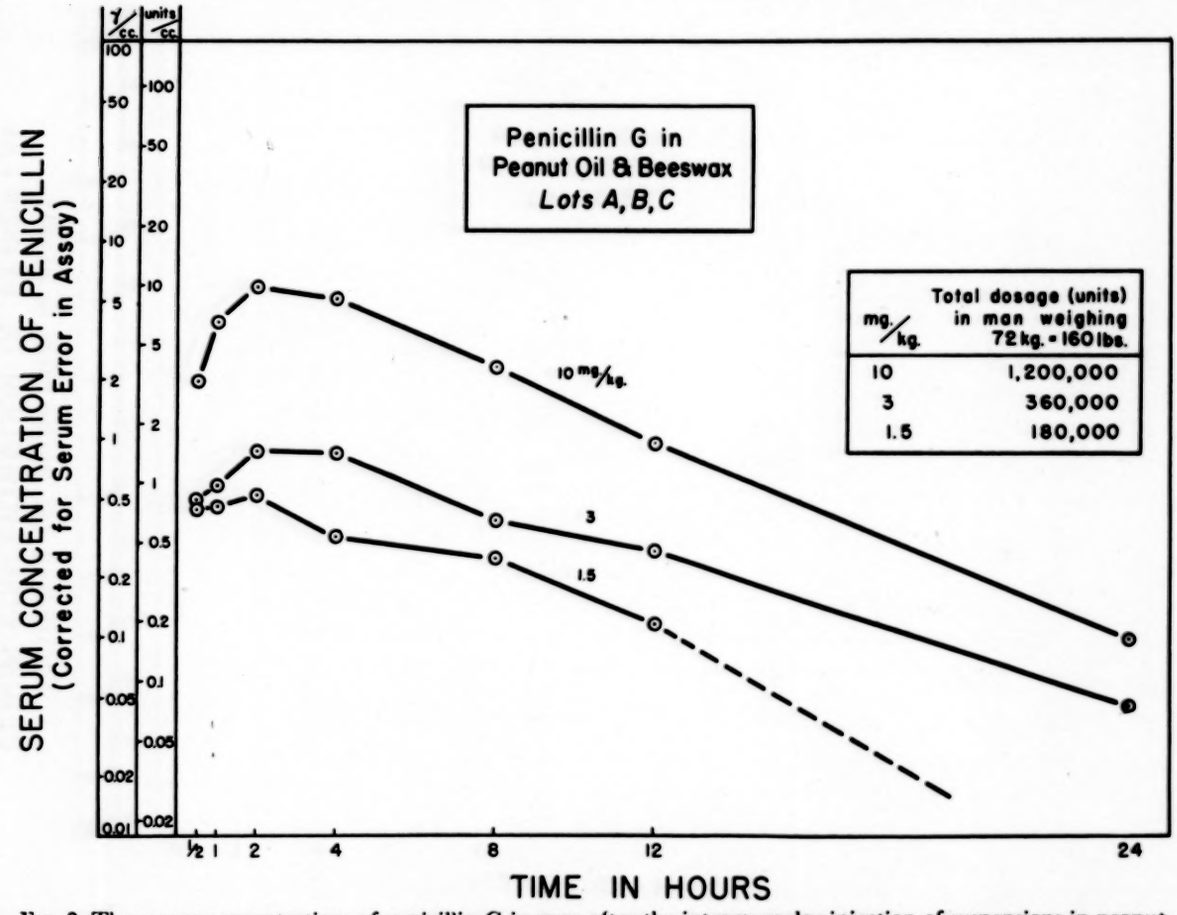


FIG. 2. The serum concentrations of penicillin G in man after the intramuscular injection of suspensions in peanut oil and beeswax. Each value in the figure is the median of nine to thirteen patients injected with easily absorbed preparations (Lots A, B and C).

in the serum at measurable levels. Thus, seven of eight patients given 10 mg./Kg. had measurable levels twenty-four hours after the injection, and at a dosage of 3 mg./Kg., eight of eleven then had measurable concentrations. After an injection of a degree of variation comparable to that observed in patients receiving the aqueous solutions; however, thereafter at every dosage level and with every preparation used there was a much greater degree of variation. (Table IIA.)

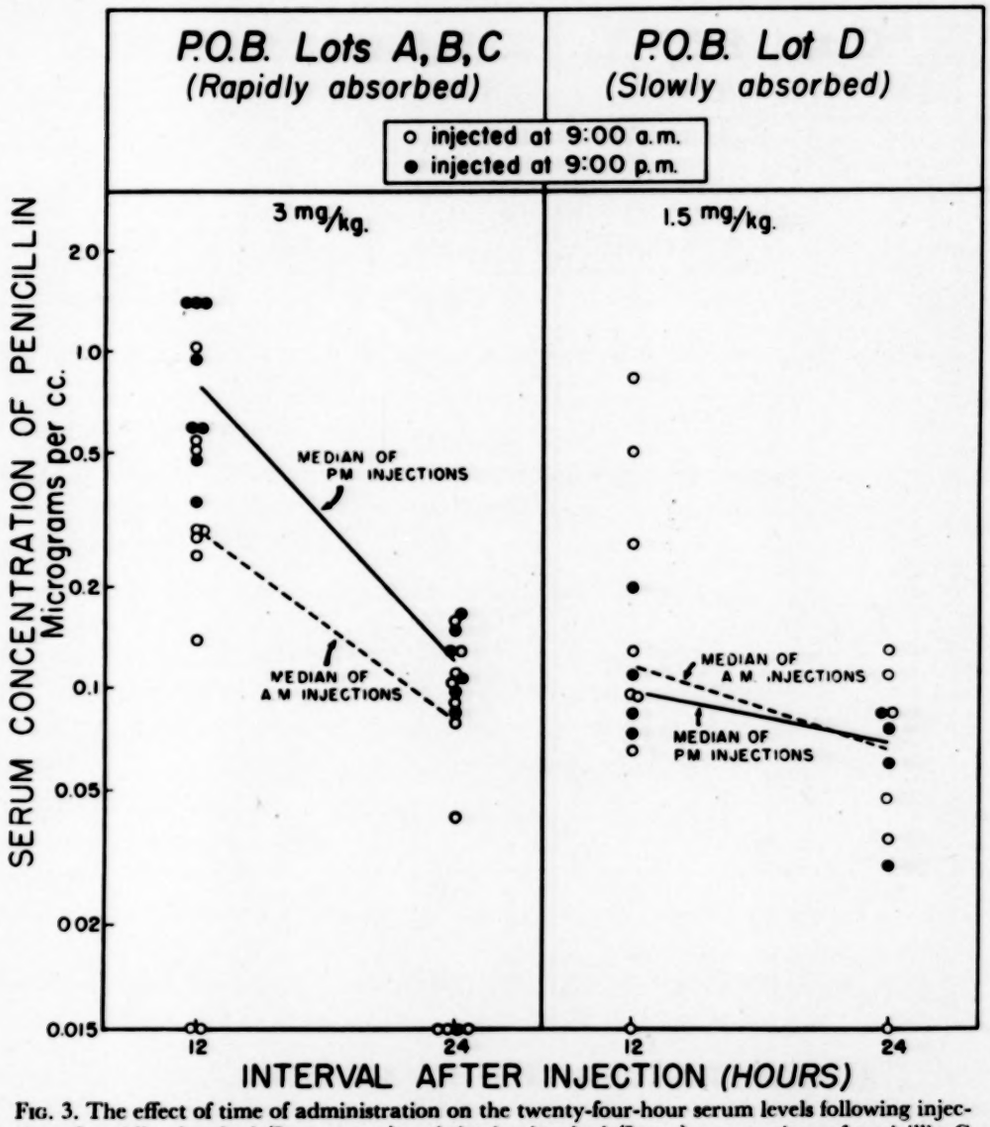


FIG. 3. The effect of time of administration on the twenty-four-hour serum levels following injection of rapidly absorbed (Lots A, B, C) and slowly absorbed (Lot D) preparations of penicillin G in peanut oil and beeswax. The lines indicate the median values in each group of patients.

1.5 mg./Kg., however, only four of seven twelve-hour sera and none of the twenty-four-hour sera contained measurable quantities of penicillin.

For the first eight to twelve hours the serum levels in patients given these particular peanut oil-beeswax suspensions showed

In confirmation of Romansky,[17] when injections were given at 9 P.M. instead of 9 A.M., consistently higher levels were observed after twelve and twenty-four hours. (Fig. 3.) This presumably reflects the fact that in the sleeping patient the site of injection is not massaged as vigorously as it is in

the waking patient. A smaller proportion is then absorbed during the first twelve-hour period, making for higher levels subsequently. (It is significant in this regard that a more recent lot of penicillin which was apparently absorbed more slowly, and series of additional patients was then run for more critical comparison, with results shown in Figure 4, Table III and Table IIIA.

This particular lot was evidently absorbed more slowly than those previously used, the serum concentration reaching a peak value

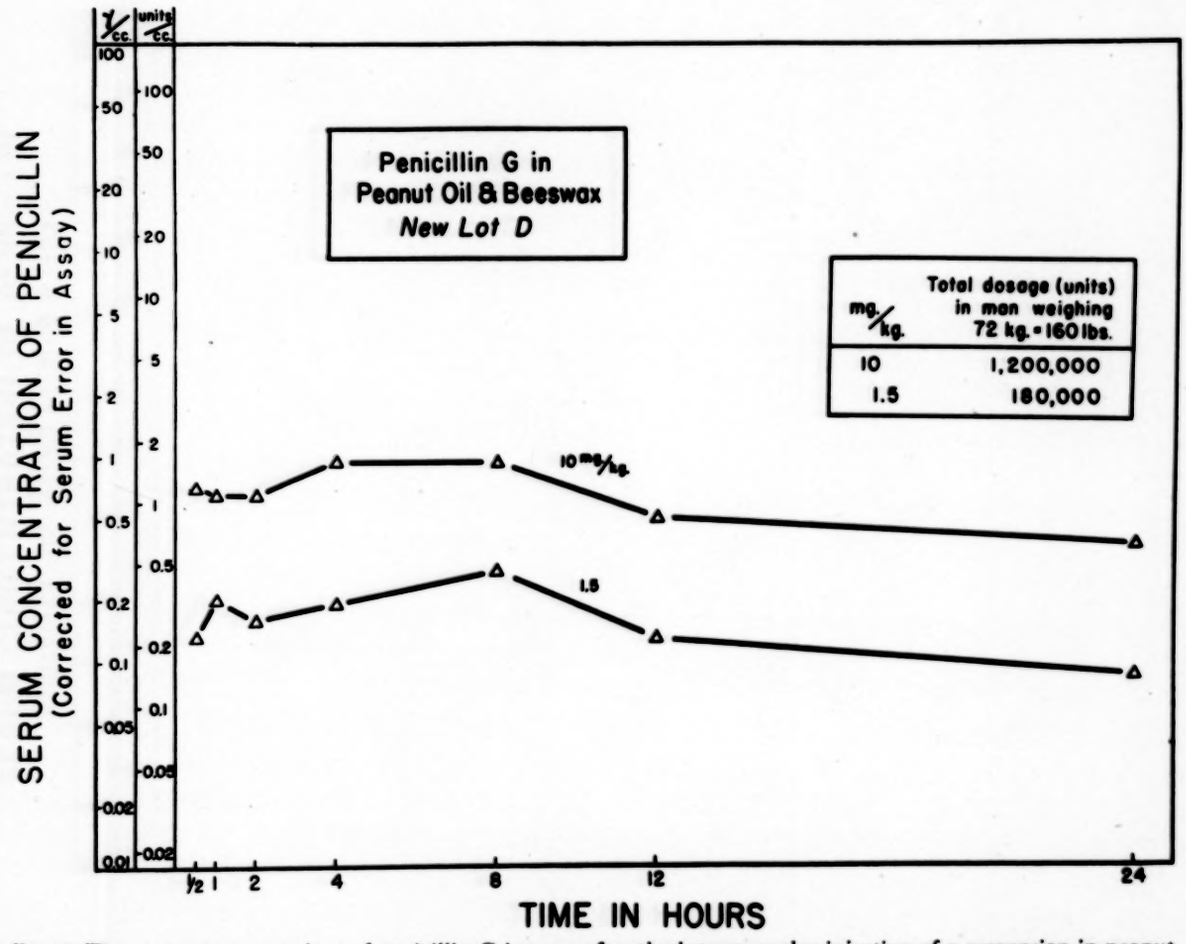


FIG. 4. The serum concentrations of penicillin G in man after the intramuscular injection of a suspension in peanut oil and beeswax. Each value in the figure is the median of six to eight patients injected with a slowly absorbed preparation (Lot D).

which gave much more sustained levels than the three lots previously discussed, did not show this difference between the morning and evening injections. (Fig. 3.)

One recent commercial lot of the peanut oil-beeswax material, here designated as Lot D, gave results which differed materially from those obtained with the three preparations previously used. It was first noted that this lot provided distinctly higher twenty-four-hour serum concentrations. A after four to eight hours instead of two hours. That peak value was uniformly lower (after 10 mg./Kg. the median peak concentration was 0.95 micrograms per cc. instead of 6.0 micrograms per cc. as with the other penicillin suspensions tested). More important, however, was the fact that the serum penicillin level thereafter fell off far more slowly so that the median serum concentration twenty-four hours after injection was 5.5 to 7.5 times higher than that

afforded by the other preparations injected in equal dosage. Thus, at 1.5 mg./Kg., five of eight patients receiving Lot D had measurable levels after twenty-four hours, averaging 0.08 micrograms per cc. With the other preparations no penicillin had been found after twenty-four hours in the serum of any of six patients receiving 1.5 mg./Kg., and levels of approximately 0.1 micrograms were attained only after the administration of 3 mg./Kg. Finally, reflecting the slow absorption of Lot D and the shape of its serum-penicillin curves, it made no significant difference in the magnitude of the

TABLE III

SERUM LEVELS OF PENICILLIN G FOLLOWING INTRAMUSCULAR ADMINISTRATION OF SUSPENSIONS IN PEANUT OIL AND BEESWAX
(LOT D SLOWLY ABSORBED)

Dosage, Mg./Kg.	No. Patients Tested	Total Dose in Man Weighing 72 Kg. (160 lbs.)		Time in Hours after Single Injection							Time in Hours after Single Injection						
				½	1	2	4	8	12	24	½	1	2	4	8	12	24
		Mg.	Units	Serum Concentrations in Micrograms per cc. (Median)							Serum Concentrations in Units per cc. (Median)						
10	6	720	1,200,000	0.71	0.65	0.65	0.95	0.95	0.50	0.54	1.18	1.08	1.08	1.60	1.60	0.83	0.9
1.5	8	108	180,000	0.13	0.20	0.16	0.19	0.28	0.13	0.085	0.21	0.33	0.27	0.32	0.47	0.21	0.14

TABLE IIIA

DEGREE OF VARIATION FROM PATIENT TO PATIENT IN THE SERUM CONCENTRATION OF PENICILLIN G FOLLOWING ADMINISTRATION IN PEANUT OIL-BEESWAX SUSPENSION
(LOT D SLOWLY ABSORBED)

Dosage, Mg./Kg.	No. Patients		Time in Hours						
			½	1	2	4	8	12	24
			Serum Concentrations in Micrograms per cc.						
10	6	Median	0.71	0.65	0.65	0.95	0.95	0.5	0.54
		Range High	2.4	2.4	2.7	3.0	1.0	1.0	0.6
		Range Low	0.5	0.15	0.11	0.1	0.3	0.12	0.1
		σ Med.	1.06	0.99	1.54	1.08	0.38	0.33	0.25
		Standard Error	0.31	0.28	0.49	0.31	0.12	0.095	0.08
1.5	8	Median	0.13	0.2	0.16	0.19	0.28	0.13	0.085
		Range High	0.55	0.25	0.16	1.0	0.96	0.51	0.13
		Range Low	<0.015	<0.015	<0.015	0.03	0.043	<0.015	<0.015
		σ Med.	0.23	0.19	0.18	0.18	0.27	0.33	0.076
		Standard Error	0.057	0.057	0.048	0.045	0.068	0.088	0.002

twelve- and twenty-four-hour serum levels whether the material was injected in the morning or evening. (Fig. 3.)

Assays of aqueous extracts showed that all four lots studied contained the amount of penicillin indicated on the labels. It

TABLE IV

FREQUENCY WITH WHICH A GIVEN DOSE OF PENICILLIN G IN AQUEOUS SOLUTION MUST BE INJECTED IN ORDER TO MAINTAIN A DESIRED PLASMA LEVEL

				To Maintain a Plasma Concentration of Penicillin G in Excess of						
Micrograms per cc.				0.1	0.2	0.5	1.0	2.0	5.0	10.0
Oxford Units per cc.				0.16	0.32	0.8	1.6	3.2	8.0	16.0
Dosage per Kg.		Total Dose in Average Adult		The Injections Indicated in the Left Hand Column Should Be Repeated at the Intervals (Hours) Indicated below in the Body of the Table.						
Mg.	Units	Mg.	Units							
10	16,700	720	1,200,000	8.0	6.0	4.5	3.5	3.0	2.0	1.2
3	5,000	216	360,000	5.0	4.0	3.0	2.0	1.6	0.6	
1.5	2,500	108	180,000	3.0	2.5	1.7	1.2	0.8		
0.6	1,000	43	72,000	2.0	1.5	0.8				
0.3	500	22	36,000	1.6	0.9					
0.15	250	11	18,000	0.9						

seems clear that as yet undefined factors (e.g., particle size of the beeswax, particle size of the penicillin and the fluidity of the mixture) may affect the rate of absorption to an extraordinary degree, evidenced both in the maximum serum concentration afforded by a given dosage and in the length of time for which the penicillin remained in the plasma and tissues at measurable levels.

DOSAGE AND FREQUENCY OF INJECTION NECESSARY TO SUSTAIN PLASMA CONCENTRATIONS OF PENICILLIN G AT A GIVEN LEVEL

From the data of Table I and Figure 1 one can by interpolation construct tables which indicate (1) how often a given dose of penicillin must be repeated or (2) what dose of penicillin must be administered at fixed intervals in order to keep the plasma concentration above a certain level (similar studies by Fleming et al.,[5] Rammelkamp and Kirby[9]). These data are given in Tables IV and V which may perhaps serve as guides to treatment. Thus, if the physician chooses to fix the amount of penicillin administered per injection and to vary the frequency of its administration, Table IV indicates how often that fixed dose should be repeated in order to provide a desired plasma level. If instead the physician wishes to keep the interval between injections fixed, then Table V indicates the dosages of penicillin which must be given at each injection in order to provide a given level for the entire interim period.

For purposes of illustration, in a patient with a staphylococcal septicemia in which the causative organism is shown to be sensitive to 0.02 micrograms of penicillin per cc. and to be killed at a maximal rate at a concentration of 0.096 micrograms, the physician may wish to maintain the plasma level at 0.2 micrograms per cc. (Present information indicates that the plasma level should be somewhat higher than the level desired in the tissues although the precise differential depends on many factors which cannot be considered in detail[13,14] and which will obviously vary from organ to organ.) In the second vertical column of Table IV alternative methods for maintaining that desired concentration are listed. A dosage of 10 mg./Kg. (1,200,000 units in the average adult) may be given every six hours, 3.0 mg./Kg. may be given every four hours, 1.5 mg./Kg. given every two and five-tenth hours, 0.6 mg./Kg. given every one and five-tenth hours or 0.3 mg./Kg. every hour. All these schedules of treatment would maintain the serum concentration at or above 0.2 micrograms per cc.

It is important to note that these intervals between injections could be appreciably lengthened and perhaps even doubled without prejudicing the outcome of treatment.[13,14] Only the total time required to effect cure might thereby be prolonged.

Again for purposes of illustration, had the organism been a strain of Streptococcus fecalis, which is killed *in vitro* only by concentrations in excess of 1.0 microgram per cc. and for which 4 micrograms per cc.

provides the maximal rate of killing, one might desire to maintain serum concentration of, e.g., 10 micrograms per cc. As seen in Table IV, it would be necessary to inject 10 mg./Kg. every hour to maintain this level. Since this represents 1,200,000 units in a patient weighing 72 Kg., continuous intravenous or intramuscular administration designed to maintain a level of 10 micrograms per cc. would probably be the method of choice.[13]

If circumstances dictate a fixed interval between injections, e.g., every four hours, the data of Table V are applicable. In a patient with a severe pneumococcal pneumonia due to an organism sensitive to 0.016 micrograms per cc. and killed at a maximal rate by a concentration of 0.096 micrograms per cc., one might wish the serum concentration to be maintained at, e.g., 0.5 microgram per cc. If the interval between injections is to be fixed at four hours, the third vertical column shows that the required dose would be 7 mg./Kg. or a total of 850,000 units in the average adult. Should the interval between injections be set at two hours, column three shows that only 1.9 mg./Kg. would be required to achieve the same effect, the individual dose representing 220,000 units in the average adult. Because of the wide margin of safety afforded by the time required for organisms to recover from the effects of penicillin, plus the body's own defense mechanisms, plus the possible persistence of penicillin in the tissues,[13,14] smaller doses than these or longer time intervals would also be effective even if they did not provide a concentration maintained at the most effective level; at the

TABLE V

AMOUNT OF PENICILLIN G IN AQUEOUS SOLUTION WHICH MUST BE INJECTED AT GIVEN INTERVALS IN ORDER TO MAINTAIN A DESIRED PLASMA LEVEL

Interval between Injections (Hours)	To Maintain a Plasma Concentration of Penicillin G in Excess of							
	0.1	0.2	0.5	1.0	2.0	5.0	10.0	Micrograms per cc.
	0.16	0.32	0.8	1.6	3.2	8.0	16.0	Units per cc.
The Following Dosages Must Be Given at the Intervals Indicated in the Left Hand Column. (Upper left hand figure in each block is dosage in mg./Kg.; lower right hand figure is the total dose in units in average adult.)								
1	0.16 20,000	0.35 40,000	0.74 85,000	1.3 150,000	2.1 250,000	4.2 500,000	9.1 1,000,000	
2	0.45 50,000	0.95 100,000	1.9 220,000	2.7 330,000	4.7 550,000	11.5 1,300,000		
3	1.2 140,000	1.9 220,000	2.9 340,000	5.7 675,000	11.5 1,300,000			
4	2.0 235,000	2.8 330,000	7.4 855,000	11.4 1,300,000				
6	5.2 600,000	8.8 1,000,000						
8	12.0 1,400,000							

smaller dosages, however, the total time required to effect cure might be significantly prolonged.

SUMMARY

1. Serum penicillin levels were studied in 138 patients following the intramuscular injection of a single dose of crystalline sodium penicillin G in aqueous solution or in peanut oil-beeswax suspension.

2. The aqueous solution was given at six dosage levels (0.15, 0.3, 0.6, 1.5, 3.0 and 10.0 mg./Kg.), totalling 18,000 to 1,200,000 units in the average adult. The median serum concentrations one-half, one, two, four, eight and twelve hours after the administration of penicillin at these varying dosages have been calculated and the pharmacologic significance of the resulting curves discussed.

3. Peanut oil-beeswax mixtures were given in dosages of 1.5, 3.0 and 10.0 mg./Kg. The high degree of variation in individual lots precluded a discussion of average or median serum concentrations provided by the preparations currently available.

4. Tables are presented which enable the physician to determine either the frequency at which a given dose should be injected or the dosage of penicillin which should be given at stated intervals in order to maintain a given concentration of penicillin in the plasma.

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Streptomycin*

A Clinical Study of Its Use in Twenty-six Cases

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WAKSMAN and Schatz[1] have reviewed the origin, production and assay, biologic and chemical properties, action, pharmacology and toxicity of streptomycin. Their *in vitro* experiments indicated that, depending on its concentration, the drug possesses both bacteriostatic and bactericidal action against many gram-negative and gram-positive organisms. Animal experiments showed its ability to control infections with organisms of the Salmonella, Brucella and Hemophilus groups. Herrell and Nichols[2] reported the results of the clinical use of streptomycin in forty-five infections which included those due to Escherichia coli, Eberthella typhosa, Aerobacter aerogenes, Pseudomonas aeruginosa, Proteus ammoniae, Klebsiella pneumoniae and Hemophilus influenzae.

In this paper we are summarizing the results obtained with streptomycin in the treatment of urinary tract infections, septicemia due to Escherichia coli, brucellosis, and Hemophilus influenzae meningitis.† The use of streptomycin in three cases of subacute bacterial endocarditis caused by penicillin-resistant strains of streptococci has previously been reported.[3]

URINARY TRACT INFECTIONS

There are nineteen cases of urinary tract infections. (Table 1.) Escherichia coli and Pseudomonas aeruginosa, either alone or in combination, were the organisms encountered. The patients were selected either because previous therapy with other agents had been ineffective or because of the acuteness and severity of the infection. Excluding Case 2, the average duration of treatment was six days. The dosage of streptomycin in most cases was 0.15 Gm. intramuscularly every three hours, a total of 1.2 Gm. each twenty-four hours. Both streptomycin hydrochloride and the sulfate were used; no difference in therapeutic efficiency could be detected. This dosage was considered satisfactory inasmuch as the urinary concentrations of streptomycin invariably exceeded 100 micrograms per cc. This concentration was found by Helmholz[4] to be adequate for inhibiting growth of bacteria in urine. Only infections due to gram-negative bacteria were treated and most of these were due to a single organism. The results were considered good in all but three cases. In Case 2, the urinary tract infection complicated a rather "brittle" case of diabetes mellitus. After fifty-five days of treatment, during which time 85 Gm. were administered, the urine still contained pus, and cultures were positive for E. coli despite the fact that urine streptomycin levels of over 1,500 micrograms per cc. were obtained by the daily administration of 4.0 Gm. of the drug. In Case 16, the urinary infection was associated with a ureteral calculus, and the urine was not rendered free of bacteria or pus although the urine streptomycin levels

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TABLE I

GENITOURINARY INFECTIONS TREATED WITH STREPTOMYCIN

Case No.	Type of Infection	Causative Organism	Days of Therapy	Total Dose Gm.	Route of Administration	Clinical Result
1	Pyelonephritis	Esch. coli	8	12.0	Intramuscular	Good; urine sterile in 48 hours
2	Pyelonephritis, cystitis	Esch. coli	55	85.0	Intramuscular Intravenous	Poor; Esch. coli and pyuria persisted in spite of intensive therapy; concomitant diabetes mellitus
3	Cystitis	Esch. coli	5	6.2	Intramuscular	Good; culture negative in 5 days
4	Pyelocystitis, left ureteral calculus	Ps. aeruginosa	7	7.5	Intramuscular	Good; urine culture negative in 72 hours
5	Cystitis	Esch. coli Ps. aeruginosa	5	6.6	Intramuscular	Good; urine culture negative in 96 hours
6	Pyelonephritis, hydronephrosis, nephrolithiasis	Esch. coli	5	5.6	Intramuscular	Good; cultures negative in 72 hours
8	Cystitis	Esch. coli	3	3.0	Intramuscular	Good; urine culture negative 5 days after therapy begun
9	Pyelonephritis	Esch. coli Ps. aeruginosa	3	4.0	Intramuscular	Good; nephrostomy done; urine negative in 5 days; associated diabetes mellitus
10	Pyelonephritis, cystitis	Esch. coli	8	10.6	Intramuscular	Good; urine negative after 7 days treatment
11	Cystitis, pyelonephritis	Esch. coli	7	8.8	Intramuscular	Good; urine culture negative 10 days following institution of therapy
12	Cystitis, pyelonephritis	Esch. coli	4	4.8	Intramuscular	Good; urine culture negative in 5 days
13	Perinephric Abscess	Ps. aeruginosa Alk. faecalis	12	15.7	Intramuscular	Good; abscess complication of nephrolithotomy; concurrent penicillin treatment
14	Cystitis	Esch. coli	9	11.9	Intramuscular	Good; urine culture negative in 4 days
15	Pyelitis, cystitis	Esch. coli	5	5.8	Intramuscular	Good; urine culture negative in 3 days; concurrent treatment with sulfasuxidine
16	Pyelitis, cystitis	Esch. coli	6	6.3	Intramuscular	Poor; infection associated with left renal calculus; Esch. coli persisted
17	Cystitis, pyelonephritis	Ps. aeruginosa	12	10.0	Intramuscular	Poor; Ps. aeruginosa persisted; associated diabetes mellitus
20	Pyelitis, cystitis	Esch. coli	7	9.0	Intramuscular	Good; associated prostatism; Rx with indwelling catheter; urine culture negative in 7 days
22	Cystitis	Esch. coli	6	6.0	Intramuscular	Good; urine negative in 6 days
23	Cystitis, pyelonephritis	Esch. coli	3	4.0	Intramuscular	Good; concurrent therapy with sulfasuxidine

ranged between 200 and 400 micrograms per cc.

The following two case reports illustrate the usual course of the successfully treated patients:

CASE 1. A male, age fifty-two, had general malaise, moderate anorexia, weakness, frequency of urination, nocturia and dysuria following a sore throat and tooth extraction one month prior to admission. Physical examination revealed nothing significant except hypertension. His blood pressure was 180/110, temperature 98.6°F. The erythrocyte count was 3,910,000, hemoglobin 14 Gm., leukocyte count 9,850, differential normal. Blood urea nitrogen was 59, creatinine 5.9 mg. per cent. Urinalysis showed albumin, many pus cells and a few hyaline and granular casts. Following an intravenous pyelogram, the patient developed a fever of 102°F., the urine became purulent and culture revealed a heavy growth of Escherichia coli. Penicillin and urotropin were administered without effect on the fever. The amount of

pus in the urine steadily increased until it constituted approximately 50 per cent of the specimen.

At this point streptomycin in dosage of 0.15 Gm. intramuscularly every three hours was started. The response was dramatic. Within forty-eight hours the urine had become clear and cultures were negative. Fever, urinary frequency and dysuria subsided rapidly. The blood urea nitrogen declined to 34.8 and creatinine to 2.3 mg. per cent. Later the urine contained an occasional pus cell and cultures showed a light growth of a gram-positive diplococcus which disappeared under penicillin therapy. While receiving streptomycin, the patient developed a troublesome pruritus and a diffuse rash which subsided when the drug was discontinued.

In this case the prompt clearing of the urinary infection was undoubtedly due to streptomycin. Duration of therapy was eight days; the total dose was 12.0 Gm. of the sulfate.

Case 15. A female, age forty-nine, developed fever, dysuria, frequency, nocturia and pain in the left lower quadrant of the abdomen radiating to the anterior and medial aspects of the left thigh two days prior to admission. A similar episode diagnosed as "cystitis" had occurred twelve years previously. Physical examination was normal except for tenderness in the left costovertebral area. Her temperature was 99.8°F., pulse 86, respirations 20 per minute. Except for a few pus cells in the urine, the findings were normal. Cystoscopic examination revealed a few small, degenerating cysts in the bladder wall. The ureteral orifices were hyperemic and edematous bullae were present. A diagnosis of subacute cystitis and ascending infection of the ureters and renal pelves was made. Urine cultures revealed a heavy growth of Escherichia coli.

Streptomycin was administered, 1.2 Gm. of the sulfate intramuscularly in dosage of 0.15 Gm. every three hours. Symptoms subsided within forty-eight hours and the patient remained asymptomatic during the remainder of her hospital stay of ten days. A total of 5.8 Gm. of streptomycin was given. Urine cultures were negative on the third day of streptomycin therapy. Intramuscular administration of streptomycin produced severe pain at the sites of injection. Moist dressings were required for relief. Upon discontinuance of streptomycin, sulfasuxidine was given in dosage of 2.0 Gm. four times daily. The patient has remained asymptomatic for nine weeks and the urine has remained clear.

BRUCELLOSIS

Live et al.[5] reported that streptomycin exerted a definite bacteriostatic effect on experimental Brucella abortus infections in guinea pigs. Herrell and Nichols[2] administered streptomycin to three patients during the acute, febrile stages of severe undulant fever but considered the results good in only one instance. In this case the spleen was considered to be a focus of reinfection and splenectomy was performed, following which the patient made a rapid recovery. They reported discouraging results in the treatment of chronic brucellosis. Three patients were treated by us; two cases were acute in which the result was apparently satisfactory, and one was chronic in which the result was discouraging. Abstracts of these three cases follow:

Case 7. E. S., a female, age thirty-seven, developed fever, which at times reached 104°F., headaches, hot flushes and profuse night sweats three weeks after returning from a trip to Mexico. She was given sulfathiazole for five days without beneficial effect upon her subjective symptoms although the fever peaks were lowered to 101° and 102°F. Because of the persistence of symptoms she was hospitalized. Physical examination was normal. The spleen was not palpable. The erythrocyte count was 5.55 million, hemoglobin 14.0 Gm., leukocyte count 5,650 with a relative lymphocytosis of 75 per cent. The sedimentation rate was 24 mm. in one hour. Serum agglutination tests against members of the Eberthella, Salmonella and Proteus groups were negative. Against Brucella abortus, agglutination was 2 plus in a dilution

of 1:1280. The brucellergin skin test was 4 plus positive. Four blood cultures were negative for members of the Brucella group. It was believed that, even in the absence of a positive blood culture, a diagnosis of acute brucellosis was justified and streptomycin was given in dosage of 0.5 Gm. every three hours for two days, 0.25 Gm. every three hours for two days, and 0.125 Gm. every three hours for nine days, a total of 45 Gm. in sixteen days. During the first three days of therapy, the maximum temperature was 101.6°F.; during the next five days it was 99.6°F., after which it remained normal. After the third day of treatment, she was asymptomatic except for occasional slight night sweats which ceased within a week. The patient has been asymptomatic for ten weeks.

Perhaps the apparently good result in this case resulted from the large daily dosage given at the outset of therapy together with continuance of therapy well into convalescence. We realize that in this disease a follow-up period of ten weeks is inadequate for a final conclusion regarding therapy. Harris[6] is of the opinion that while streptomycin may cause prompt relief of the acute stage and even produce negative cultures of blood, a relapse is likely unless local or splenic foci of infection can be removed. Subjectively the patient felt "cured" within seventy-two hours.*

The other case of acute brucellosis (Case 19) was that of a male, age forty-three, a meat trimmer, who had been ill approximately six weeks prior to admission to the hospital. Fever of the intermittent type was present. Serum agglutination was 2 plus positive against Br. bovinis in dilution of 1:640 and Br. melitensis in dilution of 1:320. The brucellergin skin test was 4 plus positive (0.04 cc.). The spleen was palpable. Repeated cultures of blood were negative. Streptomycin was administered intramuscularly as follows: 0.4 Gm. every three hours for two days; 0.2 Gm. every three hours for two days; omitted one day; 0.4 Gm. every three hours for nine days. At this point the temperature was normal, the spleen was no longer palpable and the patient felt well. After eleven days of normal temperature he was discharged. Four weeks later there were no signs of recurrence.

The result in the third case of brucellosis coincides with the experience of Herrell and Nichols[2] and Harris[6] in treating the chronic form of the disease.

Case 21. A male, age forty-three, had acquired brucellosis in 1941 at which time he was hospitalized for three months. Blood cultures were positive for Brucella abortus. Treatment consisted of foreign protein which resulted in formation of abscesses at the sites of injection. Following this he felt improved but did not regain his former state of well being. For the next three years he was able to work only a few hours each day. He always felt weak and tired and considered his efficiency greatly impaired. In 1944, he was treated with brucellin, after which a temporary improvement was noted only to be followed by periods of extreme fatigue, lassitude and drenching, enervating night sweats. No definite abnormalities were found on physical examination. The brucellergin skin test was 4 plus positive. The erythrocyte count was 3,990,000, hemoglobin 14.0 Gm., leukocyte count 6,000, with a normal differential. Serum agglutination against Brucella abortus was 2 plus in a dilution of 1:160. The sedimentation rate was 11 mm. in one hour. A chest x-ray was normal. Streptomycin was administered intramuscularly as follows: 0.3 Gm. of sulfate every three hours for seven days; 0.2 Gm. every three hours for two days; 0.15 Gm. every three hours for two days; 0.1 Gm. every three hours for eight days, a total dose of 28.8 Gm. in nineteen days. Except for an occasional rise in temperature to 100° and 101°F. (rectally) there was no change in the patient's condition. The symptoms of weakness, etc., remained. The results of therapy were poor.

INFLUENZAL MENINGITIS

Herrell and Nichols[2] obtained cures in four cases of meningitis due to Hemophilus

* Since this paper was submitted, ten months have elapsed since the patient was discharged from the hospital. She has remained asymptomatic.

influenzae. One of these patients died two months later of post-meningitis hydrocephalus. Buttre et al.[6] reported a case of influenzal meningitis in which the patient was successfully treated with streptomycin, sulfadiazine and antiserum. There are two cases of meningitis due to H. influenzae in our series.

CASE 25. The diagnosis of influenzal meningitis was confirmed by culture of the spinal fluid in a male infant, age seven months. Streptomycin was not started until the fifteenth day of the illness because of uncertainty as to the etiologic organism. Administration was as follows: 40 mg. intramuscularly every three hours and 40 mg. intrathecally daily for three days; 40 mg. intramuscularly every three hours for eleven days; 20 mg. intramuscularly every three hours for one day. The temperature became normal on the seventh day after starting streptomycin. On this day, five days after the last intrathecal injection of streptomycin, the spinal fluid streptomycin level was 2.5 micrograms per cc. and the plasma streptomycin level 10 micrograms per cc., three hours following injection of 40 mg. intramuscularly. During the period of intrathecal streptomycin administration the spinal fluid cell count increased from 1,370 to 3,800 per cu. mm., and the total protein from 80 to 175 mg. per 100 cc. Three days after the last intrathecal injection, the spinal fluid cell count was 800 per cu. mm.; the total protein had increased to 240 and the glucose from 15 to 32 mg. per 100 cc. Whether or not the intrathecal injection of streptomycin was irritating could not be determined clinically.

Recovery of the second patient (Case 21), a male age three, cannot be attributed solely to streptomycin since 6 Gm. of sulfadiazine daily were administered concurrently. In addition, anti-Hemophilus influenzae type b serum, 25 mg. of precipitable antibody nitrogen, were given on the second and 50 mg. on the fourth hospital day. However, in the opinion of the attending physician (Dr. Paul S. Rhoads) streptomycin was probably the more effective agent. H. influenzae, Type 3, was cultured from both spinal fluid and blood. The dosage of streptomycin was 0.3 Gm. intramuscularly every three hours for nine days. During eight of these days 0.05 Gm. were injected intrathecally each day. Streptomycin levels of 6.25 and 3.125 micrograms per cc. were obtained twenty-four hours after two such intrathecal injections. The serum streptomycin level on these days ranged from 6.25 to 25 micrograms per c.c. The total dose of streptomycin was 22.4 Gm.

It has been demonstrated by Zintel et al.[8] that in the normal subject streptomycin does not diffuse into the cerebrospinal fluid, but that in diseases of the meninges therapeutic levels may be reached after repeated parenteral injections. Our observations in Case 25 confirm this. In Case 21, streptomycin was administered intrathecally as well as intramuscularly because of the urgency to produce effective levels in the spinal fluid immediately.

There was no definite evidence that intrathecal injection of streptomycin is harmful.

BACTEREMIA

Herrell and Nichols[2] reported two cases of Escherichia coli septicemia which recovered following streptomycin therapy. In our case, as well as theirs, the septicemia was secondary to a urinary tract infection. (Fig. 1.)

The patient, a male, age forty-one, had a sudden onset of severe abdominal cramps and nausea. Pain later localized to the left side of the abdomen. Two days previously, gross, painless hematuria had occurred. On examination the patient complained of moderately severe pain in the left upper quadrant of the abdomen. Physical findings were normal except for tenderness in the left hypochondrium and pain on deep percussion over the left costovertebral angle. A tentative diagnosis of left renal colic was made. On admission to the hospital the temperature was 100°F., pulse 70, respiration 16. Urinalysis revealed a trace of albumin, 20 to 25 leukocytes and an occasional erythrocyte per high power field. The erythrocyte count was 4,390,000, hemoglobin 84 per cent. The leukocyte count was 10,800, with a differential of

69 per cent granulocytes and 31 per cent mononuclear cells.

On the second hospital day, the left kidney pelvis did not visualize on intravenous urography. An opacity, interpreted as a calculus, was seen in the region of the left ureter. Within six hours after the pyelogram the patient had two chills followed by a maximum temperature of 105°F. The pulse was 130. Penicillin, 30,000 units intramuscularly every three hours, was started. Blood and urine cultures were positive for Escherichia coli.

A septic temperature with a maximum of 104.4°F. continued during the next three days. Sulfadiazine was given for twenty-four hours, but was discontinued when the leukocyte count dropped to 2,050; the following day it had increased to 18,200.

On the fourth hospital day, streptomycin was begun in dosage of 0.5 Gm. intramuscularly every three hours. On this same day x-ray of the chest revealed bilateral basilar bronchopneumonia. After two days of streptomycin therapy there was definite improvement. The maximum rectal temperature was 101.4°F., pulse 80, respiration 30. On the third day of streptomycin therapy and immediately following an injection, the patient developed a moderately severe attack of "asthma" and became very excited and apprehensive. Aminophyllin, 0.5 Gm., was given intravenously and the attack subsided within thirty minutes. Later, the pa-

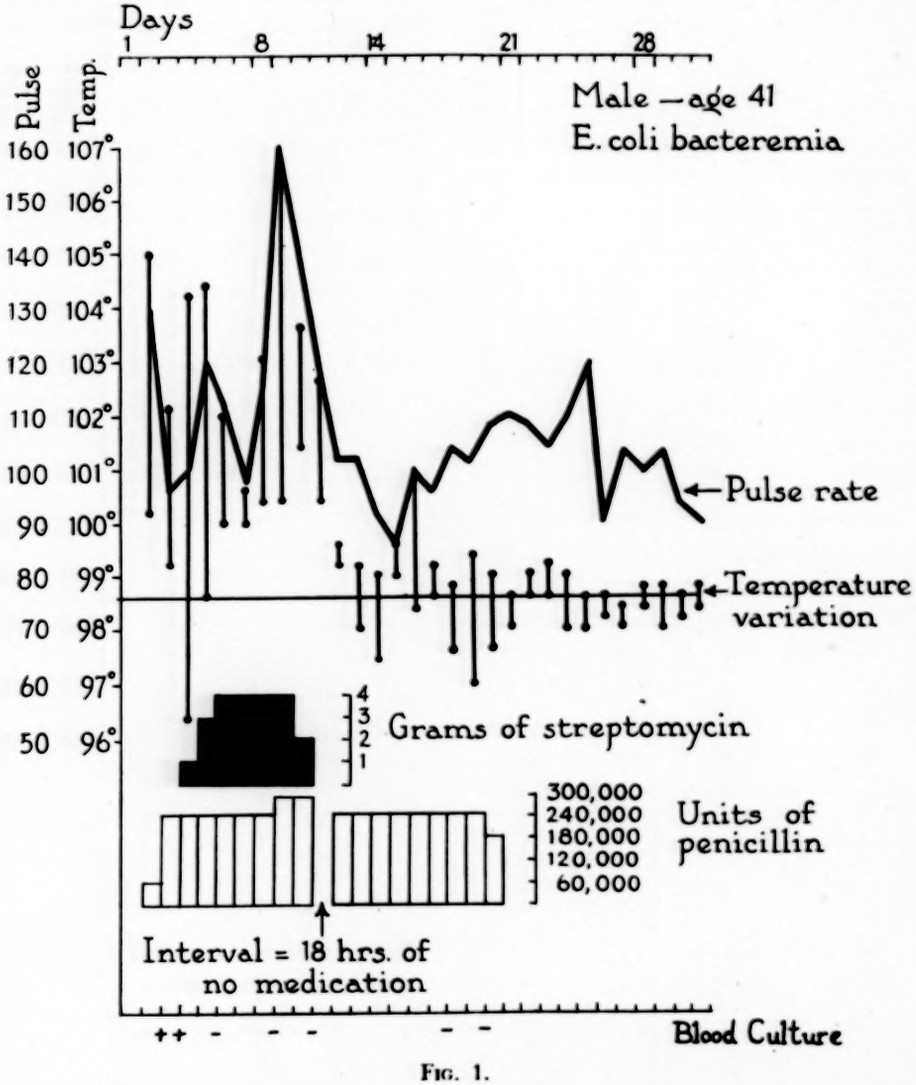


FIG. 1.

tient again became very irritable, complained of headache and developed generalized muscular rigidity including rigidity of the neck. The deep tendon reflexes, however, were normal. Spinal fluid obtained by lumbar puncture was clear and under normal pressure. The cell count was 82 leukocytes and 7 erythrocytes per cu. mm. The total protein was 21 mg. per 100 cc. Culture was negative. Later in the day the patient developed a clonic convulsive seizure lasting over twenty minutes. This was relieved by sodium amytal, 0.5 Gm., intramuscularly. The right eye was deviated laterally during the seizure, and the rectal temperature rose to 106.6°F. Another convulsive seizure occurred the next day. Spinal fluid at this time contained 62 leukocytes per cu. mm. A diagnosis of toxic encephalopathy was made, and streptomycin and penicillin were discontinued. In the meantime the pneumonic symptoms had subsided. Following the peak of 106.6°F., the temperature began to fall, reached normal within seventy-two hours (fourteenth hospital day) and remained so. Repeated blood and urine cultures were negative. Two weeks later, another intravenous urogram revealed a normal left kidney, pelvis and ureter. A total of 18.1 Gm. of streptomycin was administered.*

In this case, the portal of entry was undoubtedly the left kidney. The cause of the toxic encephalopathy could not be determined with certainty. It might have been due to either streptomycin or penicillin since the cerebral symptoms subsided when both were discontinued. Penicillin therapy was later resumed, without producing further toxic reaction. Associated with one of the convulsive episodes was a temperature of 106.6°F. which subsided rapidly when penicillin and streptomycin were stopped.

* Since this paper was submitted for publication, this patient had several attacks of chills and fever which subsided under sulfonamide medication and streptomycin, either singly or in combination. Pyuria was not always present. Repeated cultures of blood were sterile. Intravenous and retrograde urograms were repeatedly not diagnostic. On March 1, 1947 the left kidney was explored and the upper pole found to be riddled with abscesses. The kidney was removed and to date the patient has remained well.

We have seen extreme hyperpyrexia in association with penicillin therapy.[9] While chills and fever to 105° and 106°F. were frequently observed in the earlier days of penicillin therapy, convulsions and signs of toxic encephalopathy did not develop. Subsequently, as noted below, this patient received 1 Gm. of streptomycin per day without toxic reaction. It is unfortunate that both streptomycin and penicillin had to be used simultaneously in this case. It was deemed advisable to continue penicillin because of the bronchopneumonia. However, the therapeutic result as far as the septicemia is concerned must be credited to streptomycin because of the known insensitivity of Escherichia coli to penicillin, and because three days of penicillin therapy had been without effect on the septic process.

From June 1, to August 25, 1946, frequent cultures of urine revealed only Monilia. From 25 to 60 pus cells per high power field were constantly present. Intravenous urography on the latter date revealed a calculus in the left ureter at the ureterovesical junction. Meatotomy was performed and catheters inserted. Following this the temperature rose to 101°F. and culture of the urine showed E. coli. The fever did not subside and on the fourth day a severe chill occurred followed by temperature of 104°F. Repeated cultures of blood were negative. Streptomycin 1.0 Gm. per day was administered and the temperature promptly declined to normal and cultures of urine became negative. Apparently in this case there was no acquired resistance to streptomycin by the strain of E. coli.

Case 24. A female, age fifty-three, developed a septic temperature with maximum of 103°F. two days following cholecystectomy, at which a subsiding acute cholecystitis was found. Surgery was difficult because of the inflammatory process and adhesions. Oozing was trouble-

some. Penicillin, 30,000 units intramuscularly, had been given from the first postoperative day. The dosage was increased to 100,000 units every three hours on the third postoperative day. Sulfadiazine, 5 Gm. per day, was added on the fourth, fifth and sixth postoperative days without affecting the septic course. On the sixth postoperative day the patient was acutely and severely ill; her temperature was 103°F., pulse 110, respirations 24. There was pain and tenderness in the right upper quadrant and over the liver. Blood culture was negative. A diagnosis of probable pylephlebitis was made. Penicillin and sulfadiazine were stopped and streptomycin 0.15 Gm., intramuscularly every three hours started. Improvement was prompt and rapid. The patient's temperature was normal seventy-two hours later and remained so.

While the diagnosis in this case may be open to question, the fact remains that a septic process developed following surgery in which the likelihood of invasion by coliform organisms was great, and that the sepsis developed and continued in spite of penicillin and sulfadiazine but subsided promptly following administration of streptomycin.

TOXIC REACTIONS

No serious toxic effects of streptomycin were noted in these twenty-six cases. Transitory vertigo was observed in two cases. Hinshaw and Feldman[10] attribute this to a neurotoxic action on the eighth cranial nerve. Skin rashes were noted in two cases. In one, the rash was a diffuse erythema which disappeared without stopping streptomycin. In Case 2, urticarial wheals developed within a few minutes after starting an intravenous infusion containing 4.0 Gm. of streptomycin in 1,000 cc. of physiologic salt solution. Epinephrine (0.5 cc. of 1:1000 solution) afforded prompt relief. This patient had previously received 51.6 Gm. of streptomycin intramuscularly over a period of thirty-three days. The urticaria occurred upon resuming therapy after a lapse of three days. When a new lot of streptomycin was received, intramuscular therapy was again resumed without recurrence of urticaria. This suggests that the reaction was caused by some impurity in a particular lot of streptomycin rather than by streptomycin itself. Most patients complained of pain at the site of injection. The discomfort varied considerably in severity, but usually subsided within an hour after injection. Headaches occurred occasionally but these could not be definitely attributed to streptomycin.

ABSORPTION AND EXCRETION

When streptomycin is administered parenterally, the main avenue of excretion is via the urinary tract. From 50 to 75 per cent of the drug can be recovered from the urine.[11] Serum and urine levels of streptomycin were determined on most of our patients. Following the initial intramuscular dose, blood was drawn in 60, 120 and 180 minutes, and at the same intervals after the corresponding dose on the following day. Assays were done according to the method of Heilman.[12] The average, maximal and minimal levels produced by intramuscular injection of 0.15 Gm. every three hours are recorded in Table II.

Urine levels were determined by the same method. The urine was collected 30, 90 and 150 minutes following the initial intramuscular dose and after the corresponding dose the following day. The average, maximal and minimal urine levels are recorded in Table III.

Other investigators[8,11] have obtained blood levels up to 12 micrograms with repeated injections of 0.1 Gm. every three hours. It will be seen that our maximum blood levels with repeated injections of 0.15 Gm. every three hours are disproportionately higher although the mean level is about the same. Four patients receiving 0.3 Gm. every three hours had blood levels ranging from 3.125 to 80 micrograms per cc. Of fifteen

determinations, nine were from 12.5 to 25 micrograms per cc. Blood levels of 50 to 100 micrograms per cc. were repeatedly produced in one patient by 0.4 Gm. intramuscularly every three hours. This patient had moderate renal insufficiency. Our results confirm those of others that there is considerable individual variation in the blood streptomycin level resulting from the same dose, that an additive effect occurs with repeated injections and that abnormally high levels may be obtained in the presence of renal insufficiency.

TABLE II
BLOOD STREPTOMYCIN LEVELS (IN MICROGRAMS PER CC.) OF 18 PATIENTS ON DOSAGE OF 0.15 GM. INTRAMUSCULARLY EVERY THREE HOURS

Blood Sample	Average	High	Low
1 hour following initial dose	14.4	25.0	0.0
2 hours following initial dose	15.0	12.5	6.25
3 hours following initial dose	13.8	25.0	6.25
1 hour after corresponding dose next day	16.5	25.0	6.25
2 hours after corresponding dose next day	18.0	50.0	6.25
3 hours after corresponding dose next day	15.0	50.0	6.25

TABLE III
URINE STREPTOMYCIN LEVELS (IN MICROGRAMS PER CC.) OF 18 PATIENTS ON DOSAGE OF 0.15 GM. INTRAMUSCULARLY EVERY THREE HOURS

Urine Sample	Average	High	Low
½ hour following initial dose	80	400	25
1½ hours following initial dose	193	400	25
2½ hours following initial dose	280	800	50
½ hour after corresponding dose next day	375	1600	100
1½ hours after corresponding dose next day	350	800	50
2½ hours after corresponding dose next day	240	800	50

SUMMARY

Nineteen cases of urinary infection due to gram-negative organisms were treated with streptomycin. In sixteen of these the results were good. There have been no recurrences in the fourteen patients we have been able to follow over a period of one to six months. In two cases of acute brucellosis, streptomycin produced early subsidence of the symptoms and signs. No relapses have occurred in ten and five weeks, respectively. It is recognized that so short a time does not permit of a final conclusion. In one case of chronic brucellosis no demonstrable improvement occurred. One patient with Hemophilus influenzae meningitis was cured; in another case streptomycin was considered the most effective agent in producing recovery. Cure was effected in one case of septicemia due to Escherichia coli. One case of probable postoperative pylephlebitis responded dramatically. No severe toxic effects were encountered. Blood and urine streptomycin levels obtained with various doses of streptomycin are reported.

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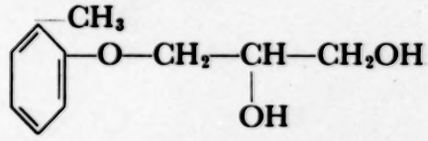
Clinical Studies in the Use of Myanesin*

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THE clinical applications of curare are based upon its ability to afford specific muscle relaxation. This property has led to increasing use of the drug as an adjuvant to anesthesia. Its value in ameliorating abnormal muscular mechanisms, i.e., muscle spasm, spasticity, rigidity and involuntary movement, is still under extensive clinical investigation.

It is commonly accepted that the chief action of curare in low concentration is at the myoneural junction. Autonomic and central synapses are affected significantly only at higher concentrations. Side effects are chiefly histaminic in type. At times these are of consequence in initiating abrupt falls in systolic blood pressure and, less frequently, in causing bronchospasm and laryngospasm. Less serious histaminic effects such as severe headache and urticarial reactions are of no concern to the anesthetist but they may interfere with treatment of neuromuscular disorders in the conscious patient.

The margin between adequate abdominal wall relaxation and respiratory failure due to curare paralysis of the muscles of respiration is not great. It is frequently necessary deliberately to invite this anesthesia complication in order to gain a satisfactory degree of relaxation. Under such conditions adequate respiratory exchange is maintained by manual compression of the gas bag until function is restored. The relative ease of reversibility of pharmacologic effects and freedom from pronounced side reactions in other organ systems has endeared the drug to many anesthetists. Nevertheless, curare is by no means the ultimate drug of choice either in anesthesia practice or in the treatment of neuromuscular disorders. Its proven value, however, has stimulated wide interest in drugs of like pharmacologic properties. This report represents a clinical evaluation, particularly in the treatment of abnormal neuromuscular mechanisms, of one such drug, myanesin, (α,β-dihydroxy [2-methyl phenoxy]-propane):*



Interest in this drug followed upon the reports of the British pharmacologists, F. M. Berger and W. Bradley[1,2] and the clinical investigations of F. B. Mallison,[3] an anesthetist. Although it has been known since 1909[4,5] that the alpha-ethers of glycerol are capable of producing paralysis, no real interest in the subject developed prior to the reports of these later investigators.

The manner in which this series of drugs came under investigation is of interest.† Dr. Berger was asked to study the pharmacologic side effects of phenoxetol which at the time was being used as a preservative for penicillin in England. He discovered that this drug had effects similar to myanesin but of a lower order. Interest being aroused, further investigations were carried out during which myanesin proved to be the most satisfactory compound tested.

Pharmacologic Data. The clinical product, myanesin, is a colorless, crystalline solid, melting at 70 to 71°c. Its solubility at 22°c. is 1.09 Gm. per 100 cc., but strong, stable,

* Supplied through the courtesy of E. R. Squibb & Sons and Abbott Laboratories.

† Personal communication.

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saturated solutions can be obtained by preparing solutions at higher temperatures and allowing them to cool. Higher concentrations necessitate the use of solubilizing agents. Among those which have been used are alcohol, propylene glycol and urea and its derivatives. With alcohol and propylene glycol a stable 10 per cent solution has been prepared which is in use in Great Britain. Solutions can be sterilized by heating and are miscible with sodium chloride, glucose and barbiturate (including thiobarbituric acid) preparations.

Previous reports are based on the use of 10 per cent myanesin in propylene glycol and alcohol. A 2 per cent solution of myanesin in normal saline was prepared in our laboratory which was stable and proved clinically effective. This preparation was used throughout this study. The adjuvants necessary to maintain solution at 10 per cent concentration obviously interfere with study of pure drug effects. In addition, there is a significantly high incidence of phlebitis following their use. Another grave contraindication lies in the production of hemolysis and hemoglobinuria[6] by higher concentrations of myanesin and solubilizing agents. The disadvantage of a 2 per cent solution lies in its bulk. Although this seems to have been considered a serious drawback to its clinical introduction in England, it has seemed to us of minor importance.

USE OF MYANESIN IN AMELIORATION OF NEUROMUSCULAR DISORDERS

Technical Data. Myanesin is so rapidly metabolized that an effective concentration, once achieved, must be maintained by constant injection of the drug since there is no significant cumulative or residual effect. The exact mode of breakdown, or the organ system involved, is not known. Urine specimens contain only small quantities of active substance even when high concentrations have been given intravenously.[7] The duration of action is brief and, without exception, is terminated within five hours after injection. The effect is usually extremely short lived and may disappear as soon as the infusion is stopped. This fact limits the therapeutic value of the drug. Other routes of injection are not feasible at present. To obtain a clinical response by oral administration, huge doses are necessary and even these have only an ephemeral and inconstant effect.

Technic of Administration. Depending upon the rate of injection, 50 to 150 cc. of 2 per cent myanesin given intravenously will afford excellent reduction of certain abnormal neuromuscular mechanisms in the adult human being. The speed and degree of effect is greatly dependent upon the rate of injection and the nature of the disease treated. In clinical use the following method has been adopted: A 2 per cent solution of the drug is started into an antecubital vein at the rate of 30 drops per minute. After one minute, if no unusual effect is seen and no subjective reactions have been reported, the rate is increased to 40 drops per minute until a therapeutic effect is obtained or certain side reactions are noted. As soon as the desired result is obtained the drip rate is readjusted to maintain an effective level without superimposition of side reactions. The patient is tested prior to injection for the presence of horizontal and vertical nystagmus. This testing continues during injection of the drug. As an effective level is approached one notes an increase in the amplitude and ease of elicitation of horizontal nystagmus. Rotary and then true vertical nystagmus appear. This roughly coincides with desired therapeutic levels in most cases and is, therefore, a useful clinical sign.

CLINICAL OBSERVATIONS DURING ADMINISTRATION OF MYANESIN

Since this drug was so recently introduced and its effect therefore still poorly understood, it may be worth while to describe the events seen in a large group of patients during the administration of increasing amounts. As previously mentioned, horizontal, rotary and vertical nystagmus are almost constantly seen as the concentration rises. At the same time, the patient may

complain of blurring of vision, probably due to extra-ocular muscle imbalance. Almost immediately, patients describe a feeling of warmth and very often of circumoral numbness, or "pins and needle" sensation. This circumoral distribution seems to correspond with the circumoral onion peel area of Dejerine-Kraus-Schlesinger. Dryness of the mouth may be noted concomitantly. There is a drop in systolic blood pressure averaging 30 mm. Hg at the same time as the subjective feeling of warmth. At this point injection of the cornea is also noted. The patient now usually describes a pleasurable feeling of relaxation and drowsiness. If injection is pushed rapidly at this juncture, the subject may go on to what appears to be natural sleep from which he can be easily aroused. Many patients during the initial injection phase become euphoric, talkative and show relaxation of nervous tension. If the patient is carefully tested at this stage, a mild degree of incoordination may be seen although no true muscle weakness is present. A small group of patients consistently note nausea; this is most pronounced when the drug is administered orally. If the drug is rapidly administered while the patient is showing the aforementioned effects, he may go through a period of increased reflexes and what appears to be decerebrate rigidity. Decerebrate rigidity has been consistently seen in animals at high drug concentration. This has been considered to be a stimulant effect of the drug but probably represents a release phenomenon based on high brain stem depression.

The pharmacology and chemistry of myanesin have not been explored sufficiently to make dogmatic statements as to the exact site and mechanism of its action. It is safe to state, however, that the drug is a spinal cord and brain stem depressant and that its effects on cortical synapses are dependent upon much higher concentrations. Although it has been shown to have some peripheral neuromuscular effect, this is not of the order of magnitude of its spinal cord depressant action. The amelioration of abnormal innervation cannot be attributed to a curare-like myoneural junction effect. Of great interest is the fact that myanesin is an efficient local anesthetic comparable to procaine. Corneal anesthesia can be obtained with surface application of the drug, but when given by injection it has a definite irritant effect.

TABLE I
CASE ANALYSIS

Mechanisms Treated	No. of Cases
Muscle spasm	25
Spasticity (abnormal stretch response)	30
Mass reflexes	16
Rigidity	8
Tremor	12
Involuntary movement (athetosis, dystonia)	10
Muscle splinting (acute anterior poliomyelitis)	2
Catatonia	2
Pain	
Neuritic	5
Causalgic	3
Convulsive movement (induced electric shock)	10

In therapeutic concentrations the chronic toxicity of myanesin is of a low order and no deleterious effects on any organ system have been noted after repeated injections. However, there is great potential danger in the use of the drug in that high concentrations or effective concentrations introduced too rapidly may lead to cardiac arrest following depression of sino-auricular node activity. Actually, the margin between cardiac effects and clinically efficient doses is very wide. The margin between good surgical relaxation and diaphragmatic paralysis is appreciably greater with myanesin than with curare. It is, therefore, obvious that the drug will be widely studied as a substitute for curare in surgical anesthesia. Since this is not the subject of the present report, it is discussed only in passing.

Clinical Data. The rapid disappearance of clinical effects together with limitations in the routes of administration unfortunately narrow the use of myanesin as an agent in ameliorating abnormal neuromuscular mechanisms. With the above facts in mind, administration of the drug was limited to the following types of cases: (1) True mussle spasm, (a) the acute low back; (2) spasticity,

(a) cord injury, (b) cerebral palsy, (c) cortical injuries; (3) rigidity, (a) parkinsonism; (4) tremor, (a) parkinsonism; (5) involuntary movement, (a) dystonia, (b) athetosis, (c) heterogenous dyskinesias; (6) miscellaneous entities, (a) acute anterior poliomyelitis, associated with limitation of range of motion of the back and extremities, with pain on such motion, (b) pain associated with nerve root compression where muscle spasm seems to be a secondary protective splinting device. Such muscle spasm is usually not completely reversible except as a result of relief of the original lesion, (c) Marie-Strümpell arthritis. (Table I.)

RESULTS

Muscle Spasm. The use of curare as a specific muscle relaxant has been applied to the treatment of acute muscle spasm of so-called "acute low-back."[9] When the disorder is not chronic and deep seated, curare has proved to be a very useful agent in reducing the muscle spasm, thereby breaking up what appears to be a vicious cycle of pain and muscle splinting. Aqueous solutions of curare are not employed for this purpose for obvious reasons, but with long-acting suspensions of curare in oil and wax a worth while result may be achieved in properly selected patients. With intravenous myanesin, relief of the acute muscle spasm occurs almost instantly, that is, within the few seconds necessary to obtain a therapeutic concentration intravenously. This dissolution of muscle spasm is abrupt, dramatic and can be obtained with concentrations which are completely safe and not characterized by muscle weakness. When the lesion is reversible, as in the "acute low-back," the desired therapeutic effect is perpetuated once good relaxation occurs. It is impossible to state with certainty that the analgesic effect of the drug does not contribute to this dramatic therapeutic effect. Nevertheless, it is sufficiently striking to be of great clinical interest.

Spasticity. It was apparent after preliminary experiments that the evanescent effect of the drug would markedly limit its usefulness in the treatment of chronic disabilities such as spasticity. The following uses were considered: (1) to evaluate the reversibility of contractures and deformities. Very often in a given patient it is impossible to state at the onset of treatment that loss of range of motion is completely reversible or partially based on fibrosis, contracture or joint changes; (2) theoretically, to afford an opportunity to reduce or prevent contractures by competent physical therapy given while the subject is under the influence of repeated injections of the drug.

In spasticity, it is possible to reduce the hyperactive stretch reflex to normal and accordingly gain complete range of motion without eliciting abnormal contractions. This reduction in spasticity is not accompanied at efficient levels by motor weakness. However, the desired effect is rapidly dissipated and on no occasion has lasted more than forty-five minutes after cessation of injection

These conclusions do not parallel those of Stephen and Chandy.[8] These investigators believed that myanesin had no effect upon spasticity following spinal cord lesions. Our experiences with spastic paraplegia following cord severance suggest that myanesin has pronounced depressant effects upon the isolated or partly isolated spinal cord.

During administration of the drug there is a marked change in reflex phenomena in the involved extremities. During the phase of muscle relaxation clonus may be brought out more easily because of the reduction in pipe-stem tension in the muscles. Depending upon the concentration of the drug in the blood stream, there may later appear increased reflex activity with new so-called pyramidal tract signs or the desired depression of abnormal reflexes. The variation in reflex status depends upon the degree of long tract depression by myanesin at the brain stem and cord levels versus local cord and brain stem depression. These findings are not in keeping with the observations of Stephen and Chandy.[8] These investigators, however, performed all

their experiments with a 10 per cent solution of myanesin in propylene glycol and alcohol. The variation in concentration of myanesin and the introduction of two pharmacologically potent solubilizing agents may account for the difference in results.

Rigidity. Rigidity, in general, responds less favorably than tremor to the drugs which are presently in vogue. It was considered of great interest to determine the effect of myanesin upon this entity. Curare had previously been shown[10] to afford no more than a modicum of reduction in the abnormal muscle tension although it occasionally was of therapeutic advantage. In patients with rigidity there appeared to be an unusual sensitivity to myanesin. It was possible routinely to release the rigidity almost completely and in effect restore the motor apparatus to normal for the duration of drug effect. Interestingly enough, the duration of effect was longer in these patients than in any other type of lesion treated, persisting up to five and one half hours. It was also possible to elicit side effects much more rapidly in lower concentrations than with any other disease entity.

Tremor. Along with rigidity it was possible to influence tremor rapidly and with small concentrations of drug. The tremor persisted longer than the rigidity and at times the tremor could be brought out by active exercise after it had disappeared at rest. In certain subjects the tremor disappeared completely for approximately the same length of time as the rigidity. In other individuals a certain suggestion of decomposition of movement persisted; or it was necessary to produce mild weakness in order to maintain absence of tremor.

Involuntary Movement. Involuntary movement responded rapidly and at safe therapeutic levels. As with tremor, there was at times a residual coarse representation of the pathologic mechanism present even though the major dyskinetic phenomena had disappeared. Again, as with tremor, the drug had to be pushed at times to a point where certain side effects occurred which interfered with patient function. In general, the immediate effect was spectacular but not prolonged beyond forty-five minutes after the presence of therapeutic levels in the blood stream.

Myanesin appears to be useful also in the treatment of athetoid crisis. A patient suffering from an acute athetoid crisis was kept completely free of motor activity throughout the administration of the drug and for forty-five minutes thereafter. The effect was at least as efficient as hypnotic doses of barbiturates and had the advantage of permitting the attending physician to deal with a conscious patient in full command of his protective reflexes.

Miscellaneous Entities. (a) During the acute stage of anterior poliomyelitis marked reduction in mobility of the truncal muscles and in range of motion of the extremities frequently occurs. Motion of the extremities is associated with extreme pain. It is felt by some clinicians that this immobility may lead to permanent deformities. Accordingly, a great deal of attention is directed against the so-called "muscle spasm" of poliomyelitis. It is not the purpose of this paper to discuss the physiologic mechanisms which underlie so-called "muscle spasm." The authors believed that by the use of a drug such as myanesin a great deal might be learned about the nature of this entity. Accordingly, subjects were chosen who exhibited frank reduction in range of motion of the lower extremities. Previous examinations had been recorded and the range of motion tested by staff therapists. The patients were then given myanesin to therapeutic levels and again tested by the same observers. At this point the muscles were noted to be relaxed to such a degree that it would be facetious to speak of "muscle spasm." The patients' demonstrable range of motion, nevertheless, was little if any increased in spite of flaccidity in the muscles. It was the impression of the experimenters that pain appeared, just as previously, at a point where there was stretching of the spinal elements: roots, root sheaths, spinal ganglia and meninges. These

observations support the view that "muscle spasm" represents protective splinting of involved spinal elements rather than true contractures of striated muscles as a primary event.

(b) In patients in whom there was true root compression, such as with herniation of the nucleus pulposus, interesting observations were made. Surprisingly, it was frequently possible to relieve completely the pain and deformities coexisting with these lesions. However, the pain invariably returned rapidly. The shortest duration of complete relief was three and one half minutes and the longest eighteen hours. These results must be interpreted as due to relief of pain by relaxation of muscle and possibly, therefore, to reduction of pressure by skeletal elements on nerve roots. On the other hand, the relief may in part be based on the analgesic effect of the drug. Preliminary investigation reveals that in states characterized by primary pain, such as neuritis, no such effect was noted.

In several patients with dislocation or partial dislocation of vertebrae pain was relieved for the duration of injection of the drug and, at times, for several hours thereafter. The usefulness of the drug in assisting reduction of such dislocations has been incompletely explored as yet. In the foregoing entities, referred pain was always dissipated almost immediately. This may prove to be useful in evaluating the underlying pathologic condition and myanesin may therefore be an important agent in the study of such lesions as the frozen shoulder, cervical disc and shoulder-hand syndrome.

(c) The exact pathologic mechanisms underlying the pain and immobility of acute Marie-Strümpell arthritis are poorly understood. Pain is excruciating at times and the accompanying muscle spasm severely limits range of motion. The prolonged loss of range of motion possibly exerts a deleterious effect on muscle length, blood supply and the possibility of restoration of normal skeletal mechanics. Since the pathogenesis of the disease is obscure, it was believed to be of interest to try myanesin in acute Marie-Strümpell arthritis. It was reasoned that if the pain were due to extreme muscle splinting or spasm rather than to an inflammatory or neuritic phenomenon, it might be resolved by muscle relaxation. Diagnosis in the first patient chosen was verified by three competent observers. Pain could not be controlled by traditional means and at the time the patient was first seen the act of moving from a bed to a stretcher was too excruciating to be borne. The patient was given intravenous myanesin and within thirty seconds after vertical nystagmus had appeared he was completely free of pain and could flex and extend his extremities and his truncal muscles freely. The intravenous injection was discontinued after the injection of 150 cc. of the drug and the patient was allowed out of bed. At this time his range of motion was normal and could be carried out without pain. Further treatment of this patient consisted in maintenance of some degree of muscle relaxation with curare in oil and wax. Continuous progress in such patients is of interest since long-term follow-up examinations should reveal the presence or lack of development of typical vertebral changes. If these latter do not appear, their pathogenesis may in part be blamed upon the early acute muscle spasm and accompanying loss of range of motion. The acute experiment described, however, suggests only that pain is based on muscle spasm rather than on inflammatory neuritis or compression of nerve roots.

GENERAL OBSERVATIONS

In a large series of subjects 2 per cent myanesin was used with a wide margin of safety. No respiratory depression was noted, no cardiac effects, no dramatic drop in systolic blood pressure and no significant changes in vital signs. At no time was hemoglobinuria induced even after repeated injections. Likewise, phlebitis did not occur although the same vessels were repeatedly used. Electrocardiograms at therapeutic drug levels showed no deviation from the previous pattern and no changes in cardiac

function were demonstrated on examination. Although myanesin in large doses is capable of depression of cortical potentials, test subjects showed no electroencephalographic changes at the time they exhibited maximal relief of their clinical syndrome.

On the other hand, incoordination, lassitude and blurring of vision very often restricted the possibility of getting a patient out of bed after administration of the drug. By the time all of these signs had disappeared the desired clinical effect usually was lost.

COMMENTS

The properties of myanesin place it in an unusual pharmacologic niche. Although its chief sites of action seem to lie in the spinal cord and brain stem, it has many other properties. At certain concentrations it has definite hypnotic effect, at others it is an effective local anesthetic. Its curare-like action seems of minor import but its ability to depress cortical potentials relates it more closely to the barbiturates. Its efficiency in ameliorating involuntary movement, rigidity, spasticity and tremor are of a higher order than that of the curare series, and at least comparable to any known therapeutic agent. Its site of action in the brain stem possibly contributes to its unusual efficiency in these disorders. Unfortunately, the evanescent nature of its effects makes it more of a laboratory tool than a therapeutic agent, except in certain specific instances. Toxic manifestations have been fairly well outlined. At high concentrations the drug has a quinidine-like action, prolongs the refractory period of cardiac muscle and may critically depress sino-auricular node activity and lead to ventricular standstill. These cardiotoxic concentrations lie outside the realm of therapeutic needs and the margin of safety is comfortably wide. The production of hemolysis limits the use of high concentrations of the drug. Solubilizing agents are necessary to maintain such concentrations and these are undesirable. In 2 per cent solutions neither hemolysis nor phlebitis has been a problem. At present the use of myanesin seems limited to the intravenous route of administration. Oral administration yields completely unpredictable results with inefficient therapeutic effects at best. Oral administration seems to cause a greater incidence of nausea than any other route of administration. Intramuscular injection of myanesin in concentrations higher than 2 per cent leads to necrosis and evidence of severe inflammatory reaction in the tissues. These changes do not occur when a 2 per cent solution is used. The bulk necessary for effective doses of 2 per cent solution by the intramuscular route makes such a technic of administration unfeasible. Chronic changes incident to prolonged use of the drug have not been noted as yet and there is no demonstrable toxic effect on any organ system incident to such use. The exact mechanism of breakdown of the drug in the body is not understood. Unlike curare, it is almost completely metabolized and little is put out in the urine intact.

Myanesin is a simple drug to synthethize and one which entails no great expense in manufacture. A great many analogues have been studied but as yet none of this series of drugs has shown any positive advantage over myanesin.

One of the great drawbacks to the proper evaluation of curare lies in the difficulty of ascertaining blood concentrations. Efficient methods of determining myanesin blood levels[7,11] have already been described.

The use of myanesin clinically for treatment of reversible muscle pathologic disease such as muscle spasm seems practical and efficacious. Its value as an aid in manipulation of painful contractures and dislocations deserves further investigation. It should prove of great worth in the proper evaluation of muscle deformity and contractures.

In effective therapeutic concentrations few of the known toxic effects have been seen. Certain entities have proven more sensitive to the drug and in these there has been more rapid appearance of side effects. This has been particularly true in parkinsonism and less markedly so in athetosis. The residual effects in parkinsonism were

maintained for a longer period than in any other condition treated. It is the authors' opinion that this drug will not replace curare in the treatment of spasticity and rigidity since prolonged duration of effect cannot be maintained. Its usefulness in anesthesia was not sufficiently explored in this study to venture any opinion as to its effectiveness in that sphere. However, the degree of synergism between myanesin and the barbiturates is striking and undoubtedly will increase the value of the drug as an adjuvant to intravenous pentothal anesthesia.

CONCLUSIONS

1. Myanesin in 2 per cent solution is capable of affecting the abnormal neuromuscular mechanisms underlying muscle spasm, spasticity, rigidity, tremor and the dyskinesias.

2. The primary site of action of this drug appears to be the brain stem and spinal cord.

3. In addition to its spinal cord and brain stem depressant action, the drug has local anesthetic activity of the order of procaine and in certain concentrations has a hypnotic effect of the order of the barbiturates.

Although it is known that myanesin has a curare-like action peripherally, this is of a low order and is not responsible for the major pharmacologic effects of the drug.

4. The margin of safety with 2 per cent solutions seems sufficiently wide to make the drug of therapeutic value.

5. At such concentrations, neither hemoglobinuria nor phlebitis was produced.

6. During administration of 2 per cent myanesin in the human subject the following side-effects have been regularly noted: (a) horizontal nystagmus, (b) a feeling of warmth, (c) circumoral numbness or "pins and needles" sensation, (d) a mild fall in systolic blood pressure, (e) corneal injection, (f) vertical nystagmus, (g) blurred vision, (h) dry mouth, (i) euphoria, (j) slight general muscular incoordination and (k) drowsiness.

7. Myanesin is worthy of further trial as a therapeutic agent in the treatment of true muscle spasm.

8. In the treatment of other neuromuscular entities myanesin seems of great academic interest but of limited clinical value.

9. The neural mechanisms underlying parkinsonism seem to be particularly sensitive to the action of the drug.

10. The use of myanesin in eliciting basic mechanisms underlying the changes of acute poliomyelitis and Marie-Strümpell arthritis is described.

11. Myanesin is suggested as a useful agent in evaluating the nature of muscle contractures and deformities in a wide variety of conditions.

12. Further studies of its pharmacologic effects are necessary.

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Correlation between the Effect of Quinidine Sulfate on the Heart and Its Concentration in the Blood Plasma*

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In recent years, the importance of the relationship between the concentration of a drug in the blood and the intensity of its effect has been recognized and many such correlation studies have been made. Most of these studies, however, have been devoted to the action of drugs like the sulfonamides and penicillin, whose main site of action is probably the blood and body fluids. When a drug is used for its effect upon tissue cells, for example quinidine for its effect on the heart, the problem becomes more complicated. Obviously, in trying to understand fully the quantitative aspect of the effect of such a drug, the first problem is to establish the relationship between the concentration of the drug in the heart muscle and the intensity of the effect the drug has on the heart. The second step is to establish the relationship between the concentration of the drug in the blood and its concentration in the heart muscle.

To determine the relationship between the blood and tissue concentration of a drug and the effect it has on an organ, it is necessary to have a method of determining the concentration of the drug in the blood and in the organ and also a method of quantitating the effect that the drug has on the organ. Methods of estimating quinidine in the blood and tissues are now available[1] and the measure of the variations of the rate of the circus movement in auricular fibrillation offers a method of quantitating the effect quinidine has on the heart or at least on the auricles.[2] As permanent auricular fibrillation cannot be reproduced in animals, it is impossible to use animal experimentation in order to correlate the concentration of quinidine in the blood, the concentration of quinidine in the atrial muscle and the effect of quinidine on the circus movement of the fibrillating auricles. Furthermore, since it is not feasible to determine the concentration of quinidine in the auricular tissue of patients, the only approach is to study in patients with chronic auricular fibrillation the correlation between the effect of quinidine on the rate of the circus movement and the concentration of quinidine in the blood.

It is the purpose of this paper to report, in the first part, observations made on patients of the relationship between the concentration of quinidine in the blood plasma and the intensity of the effect of the drug upon the heart as measured by the changes of the rate of the circus movement in auricular fibrillation. In the second part are reported the results of studies made on dogs in an attempt to correlate the concentration of quinidine in the blood plasma and its concentration in several tissues including atria and ventricles.

STUDIES MADE ON HUMAN SUBJECTS

Methods. The concentration of quinidine base in the blood plasma and in tissues was determined by the method of Brodie, Udenfriend, Dill and Downing.[1] The rate of the circus movement in the auricles was determined by the method first suggested by Lewis.[2] Two non-polarizable electrodes

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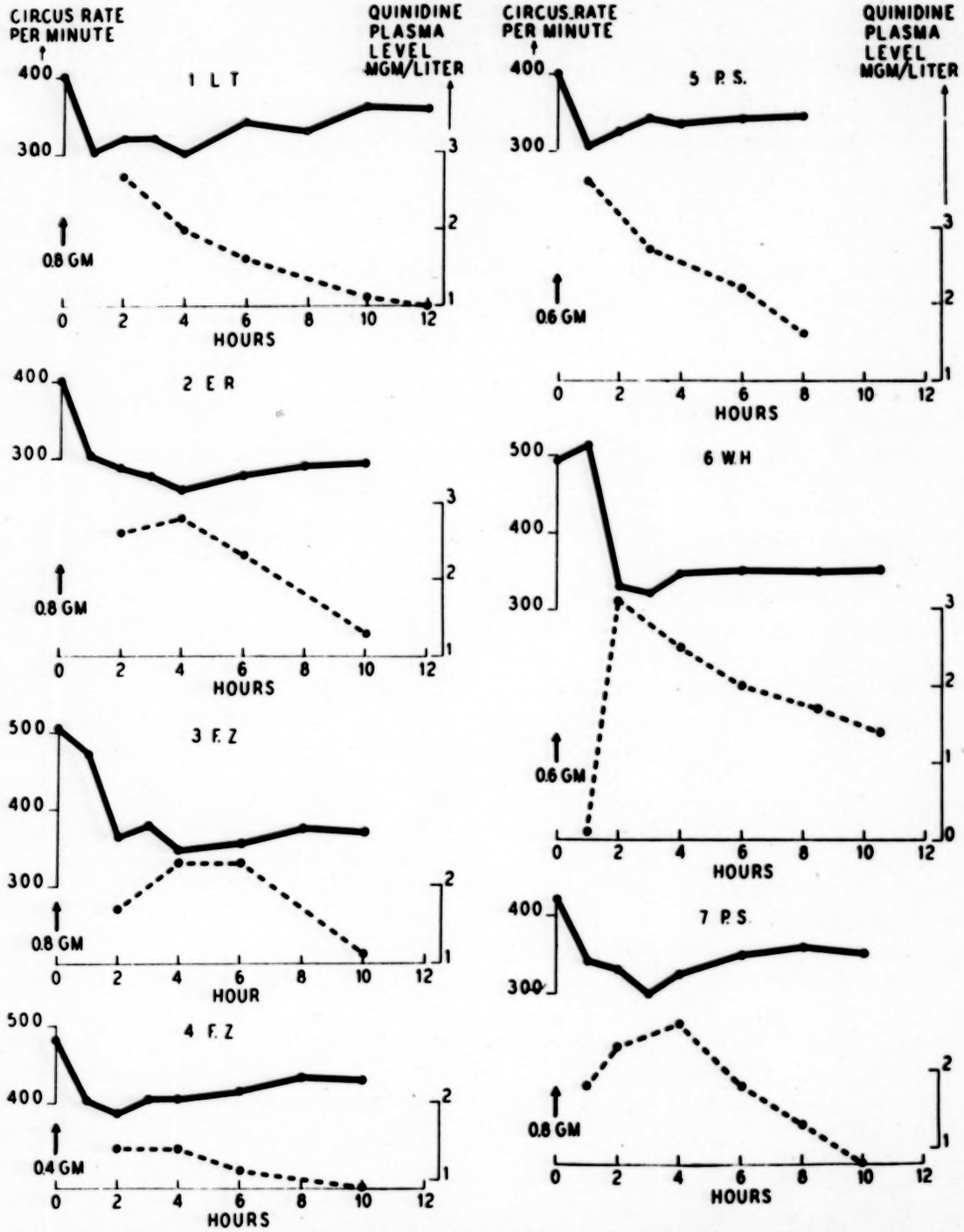


FIG. 1. Correlation between the quinidine plasma level and the effect of quinidine on the rate per minute of the circus movement in chronic auricular fibrillation in seven studies on five patients. In each study the upper curve is the rate of the circus movement per minute, the lower curve the quinidine plasma level expressed in mg. of the base per liter. Time in hours. The arrow in each experiment indicates the time at which quinidine sulfate was administered orally and the figure under each arrow is the dose of quinidine sulfate given.

were placed on the chest along the right sternal border and connected to the electrocardiograph. Their optimal location varied slightly in different patients. Having once determined in a given patient the points at which maximal deflections of auricular origin were obtained, the location of the electrodes was kept constant. Patients were selected in whom the auricular fibrillation was of a coarse type so that good deflections due to auricular activity were obtained in the precordial derivation used. Unfortunately, relatively few such patients are available as auricular fibrillation of such a type is uncommon in chronic auricular fibrillation. It is most common in paroxysmal auricular fibrillation and auricular fibrillation of recent onset but such patients in the course of quinidine therapy, even with small doses, frequently revert to regular sinus

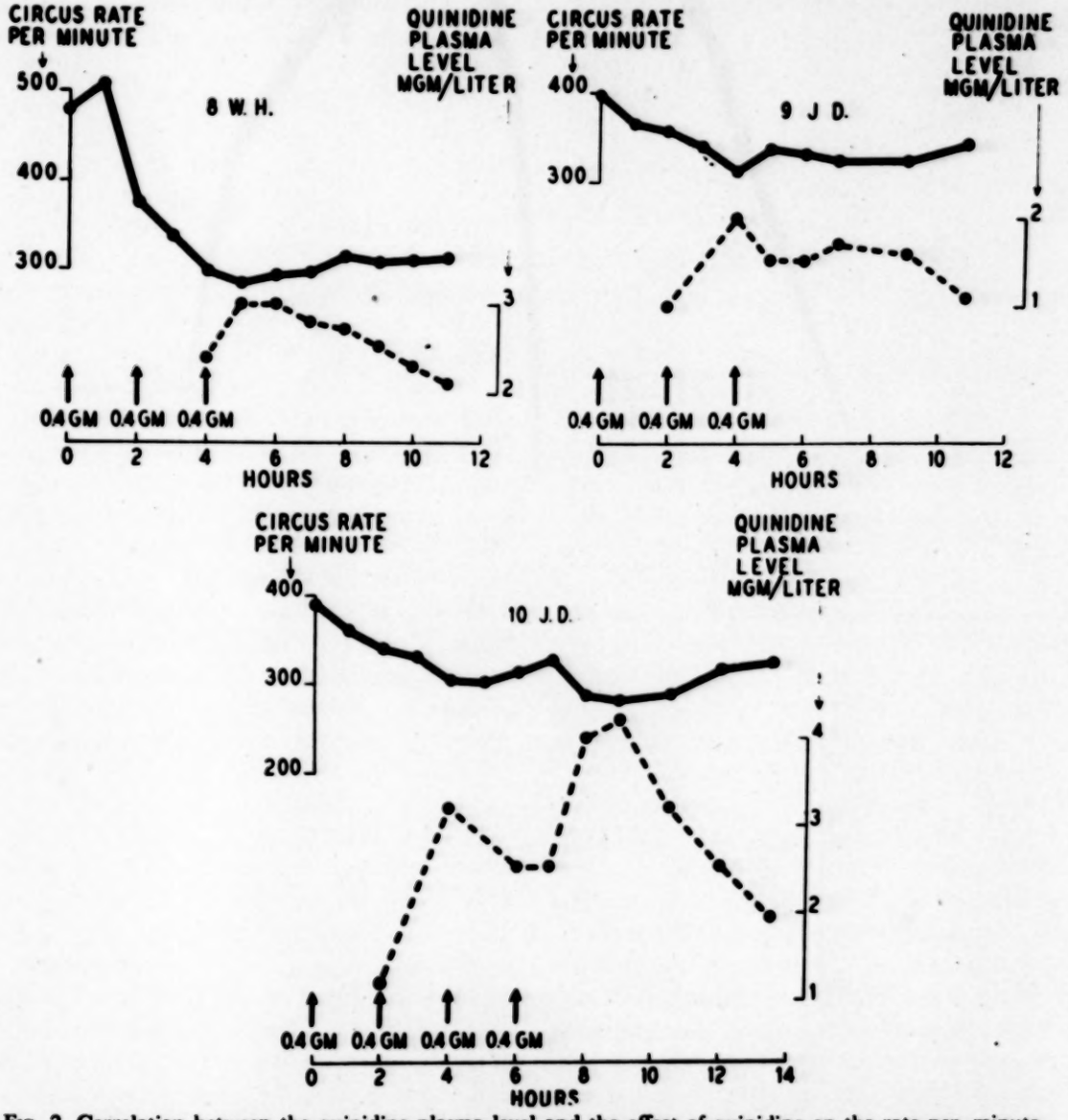


FIG. 2. Correlation between the quinidine plasma level and the effect of quinidine on the rate per minute of the circus movement in chronic auricular fibrillation in three studies on two patients. In each experiment the upper curve is the rate of the circus movement per minute, the lower curve the quinidine plasma level expressed in mg. of the base per liter. Time in hours. The arrow in each experiment indicates the time at which quinidine sulfate was administered orally and the figure under each arrow is the dose of quinidine sulfate given at the arrow.

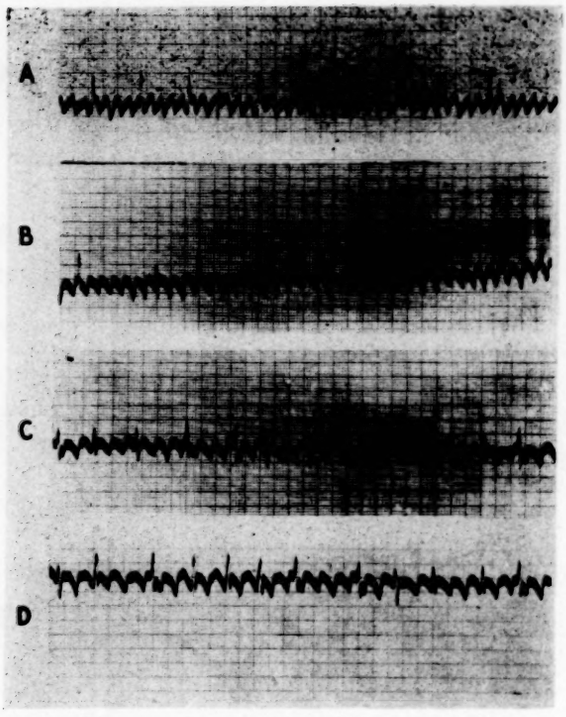


FIG. 3. Chest leads of study 10. The patient received 0.4 Gm. quinidine sulfate at 9 A.M., 11 A.M., 1 P.M., and 3 P.M. A, control record taken at 9 A.M.; circus rate 391 per minute. B, record taken at 11 A.M.; circus rate 340 per minute. C, record taken at 1 P.M.; circus rate 305 per minute. D, record taken at 5 P.M.; circus rate 287 per minute.

rhythm, thus terminating the study prematurely. The patients were fully digitalized at least two weeks before the administration of quinidine, placed on a maintenance dose of digitalis at least one week before the study was begun and were kept on a maintenance dose of digitalis throughout the quinidine study. Each patient received a test dose of 0.2 Gm. quinidine sulfate a few days before the study was begun to screen out patients with idiosyncrasy to the drug. The patients were kept in bed during the observations. A control electrocardiogram was taken the day before the quinidine study. The day of the study, after a control electrocardiogram was taken, the patient was immediately given the dose or the first of repeated doses of the drug; then electrocardiograms and blood samples were taken at various intervals. When repeated doses were given, each additional dose was administered immediately after an electrocardiogram and a blood sample had been taken. When the same patient was used more than once, a period of at least eight days was always allowed to elapse between periods of study.

Results and Discussion. Ten studies were made on six patients. In the first seven studies made on five patients (L. T., E. R., F. Z., P. S., W. H.), a single dose of quinidine sulfate was given. (Fig. 1.) In the last three studies performed on two patients (W. H., J. D.), repeated doses of quinidine sulfate were given, 0.4 Gm. every two hours for three doses in two studies and 0.4 Gm. every two hours for four doses in the last study. (Fig. 2.) Figure 3 shows electrocardiographic tracings obtained in the tenth study before and after the administration of quinidine.

In analyzing the results obtained after the oral administration of a single dose (Fig. 1), it is obvious from the curves representing the rate per minute of the circus movement and the plasma quinidine concentration that the effect on the circus rate is roughly parallel to the plasma quinidine concentration. For example, the maximal cardiac effect is obtained within four hours and the maximal quinidine level is also reached within four hours. This parallelism between quinidine plasma concentration and cardiac effect of the drug has also been observed recently by Linenthal, Ulick and Patterson[2] and by Delevett and Poindexter.[4] However, if our results are scrutinized more closely, it is apparent that there is no strict quantitative relationship between the cardiac effect and the plasma concentration of quinidine. In the second study, for example, two hours after the oral administration of 0.8 Gm. of quinidine sulfate, the circus rate fell from 402 to 285 per minute and the plasma concentration of quinidine was 2.6 mg. per liter, whereas ten hours after the administration of quinidine, the circus rate was practically the same, 292 per minute, but the plasma concentration of quinidine was only 1.3 mg. per liter, i.e., much lower than two hours after the administration of the drug. In the third study, the circus rate was the same, i.e., 364 and 371 per minute, two hours and ten hours respectively, after

the oral administration of 0.8 Gm. of quinidine sulfate but the plasma concentration was 1.7 mg. per liter two hours after the administration of the drug and only 1.1 mg. per liter ten hours after the administration of the drug. The fifth, sixth and seventh studies also show similar discrepancies. (Table 1.)

TABLE 1*

Study No.		Circus Rate Per Minute	Quinidine Plasma Level in Mg. Per Liter
2	Control	402	
	2 hours after administration of 0.8 Gm. quinidine sulfate	285	2.6
	10 hours after administration of 0.8 Gm. quinidine sulfate	292	1.3
3	Control	505	
	2 hours after administration of 0.8 Gm. quinidine sulfate	364	1.7
	10 hours after administration of 0.8 Gm. quinidine sulfate	371	1.1
5	Control	401	
	3 hours after administration of 0.6 Gm. quinidine sulfate	342	2.7
	8 hours after administration of 0.6 Gm. quinidine sulfate	346	1.6
6	Control	497	
	4 hours after administration of 0.6 Gm. quinidine sulfate	345	2.5
	10 ½ hours after administration of 0.6 Gm. quinidine sulfate	351	1.4
7	Control	422	
	1 hour after administration of 0.8 Gm. quinidine sulfate	342	1.8
	10 hours after administration of 0.8 Gm. quinidine sulfate	352	0.8

* Table summarizing the main discrepancies between quinidine plasma level and intensity of the cardiac effect observed in studies of Figure 1.

In the eighth, ninth and tenth studies (Fig. 2) repeated doses of quinidine were given. The reasons for making these studies were that quinidine sulfate is usually administered to patients in repeated doses and also that it was hoped that such experiments might help in understanding the results observed in studies in which one single dose was given.

The only difference between the results observed in the studies of Figure 1 and the studies of Figure 2 as to correlation between quinidine plasma levels and intensity of the cardiac effect of the drug* is that only one definite discrepancy between plasma level and intensity of cardiac effect was observed: In the eighth study, the cardiac effect four and seven hours after the last dose of quinidine was the same in intensity whereas the corresponding plasma levels were, respectively, 2.7 mg. and 2.1 mg. per liter. The difference between the results obtained in the two sets of studies may be more apparent than real. Indeed, had we followed our patients longer in the eighth, ninth and tenth studies, i.e., as long after the last dose as we followed them after one single dose in the first seven studies, it is possible that more marked discrepancies would have been observed.

Although the relationship between plasma and heart muscle concentration of quinidine has not as yet been established, it seems profitable to consider a number of factors that theoretically may be responsible for the discrepancies observed between the quinidine plasma level and the intensity of the effect of the drug on the heart. It may be first postulated that when, due to the action of quinidine, the rate of the auricular circus movement has been lowered to a certain level and has remained at the same level a few hours later, the concentration of the drug present in the auricular muscle remains approximately constant. For example, in the second study, the circus rate

* Comparison between the intensity of the cardiac effect of quinidine when it is given in single and in repeated doses without attempting to correlate the cardiac effect to plasma levels is the subject of a previous paper now in press.

was 285 per minute two hours and 292 ten hours after the administration of 0.8 Gm. of quinidine sulfate. Although at these two moments the quinidine plasma level was, respectively, 2.6 mg. and 1.3 mg. per liter, it might be assumed that the concentration of quinidine in the auricles was the same. If so, the reason for the discrepancy between tissue level and plasma level is not clear. *A priori*, it could be due either to a plasma level relatively higher than the tissue level two hours after the administration of the drug or to a plasma level relatively lower than the tissue level ten hours after the administration of the drug. If the plasma level, soon after the administration of the drug, is relatively higher than the tissue level, it is possible that at the plasma level observed the auricular tissue has fixed all the quinidine it can. The nature of this process of fixation and the laws that govern it are clearly beyond the scope of this investigation. It also may be that a time factor is involved and that the period during which the auricular muscle was exposed to the high plasma level of quinidine was too short to allow the establishment of as high a tissue level as could be expected from the plasma level. The two explanations do not exclude one another. In short, if the discrepancy between tissue and plasma quinidine levels is due to too high a plasma level during the first few hours that follow the drug administration as compared to its tissue level, it could be due to the fact that the auricular muscle has fixed all the quinidine it can at the plasma levels observed and with the time during which the auricles were exposed to such plasma levels. Another explanation, not exclusive of the first possible explanation just mentioned, is that the plasma level is too low in relation to the tissue level when the plasma level of the drug decreases. This will occur if the heart retains quinidine longer than the plasma and the fifth, sixth and seventh studies seem to suggest this as a definite possibility if the initial postulate is correct that equal cardiac effects mean equal concentration of quinidine in the heart muscle.

On the other hand, the postulate originally made that equal cardiac effects mean equal cardiac quinidine concentrations may very well not be correct. In the second study for example, although the cardiac effect is of the same intensity two hours and ten hours after the administration of the drug, the cardiac concentration of quinidine two hours after the drug administration may well be different from that ten hours after the administration. If the concentration of quinidine in the auricles two hours after the administration of the drug is higher, it would seem that the cardiac effect is not more marked after two hours because there is a maximal cardiac response to quinidine beyond which a further increase in the cardiac concentration of quinidine produces little or no further effect on the heart. Whether or not the problem is further complicated by the fact that all or part of the effect of quinidine is due to its products of degradation and the intensity of its effect determined therefore by the rate of degradation, it is not possible to state from these experiments. Furthermore, the possibly active degradation products of quinidine may not be fluorescent, which would be another complicating factor, as the method we used to determine the quinidine concentration in plasma and tissues is based on the property of quinidine of being fluorescent.

To summarize, as explanations for the discrepancies observed between the plasma quinidine level and the intensity of the cardiac effect of the drug, there are several possibilities: (1) the plasma level in the first few hours after the oral administration of the drug is too high as compared to its auricular level because the auricles become saturated at relatively low plasma levels; (2) the plasma level in the first few hours is too high as compared to its auricular level because the time during which the auricles are exposed to a high plasma level is too short and therefore the auricles do not fix as much quinidine as might be expected from the height of the plasma level; (3) the plasma level later in the period of action of the drug is too low as compared to its

auricular level because the auricles retain quinidine longer than the plasma and (4) the auricular level early in the period of action of quinidine is commensurate with the plasma level but the cardiac effect is not more marked because the increment of the

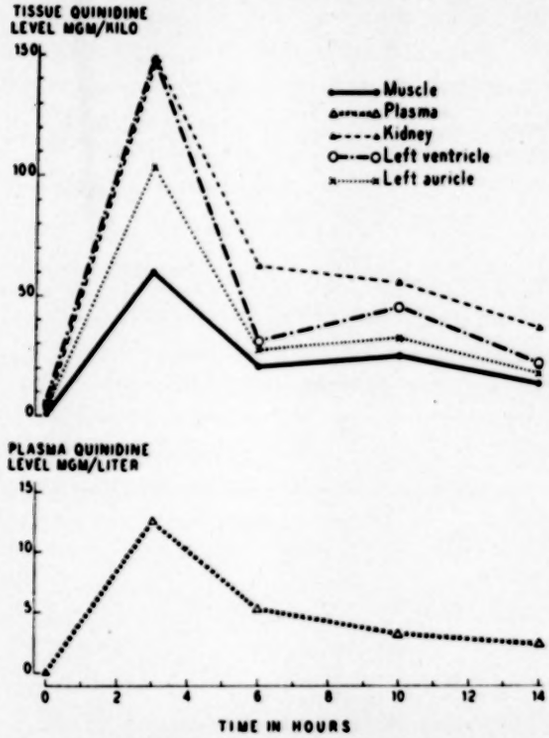


FIG. 4. Arterial plasma quinidine level expressed in mg. of the base per liter, and quinidine levels expressed in mg. of the base per Kg. in striate muscle, left auricle, left ventricle and kidney in five dogs at the time they were sacrificed. One dog was used as a control, received no quinidine and was sacrificed at 9 A.M. The other four received 50 mg. quinidine sulfate per Kg. of body weight at 9 A.M. and were sacrificed respectively three, six, ten and fourteen hours after the administration of quinidine.

cardiac effect decreases and tends toward zero with any further increment of the auricular level.

STUDIES MADE ON DOGS

Method. To determine which of the explanations mentioned is responsible for the discrepancies between the quinidine plasma level and the intensity of the cardiac effect as measured by the effect on the rate of the circus in auricular fibrillation, a series of experiments was performed on dogs in an attempt to establish the relationship between quinidine plasma level and quinidine tissue level. Plasma and tissue quinidine levels were determined with the method referred to previously.[1] First, a series of five dogs was used. All the dogs fasted for twenty-four hours and were fed ground meat at 9 A.M. One dog, used as a control, received

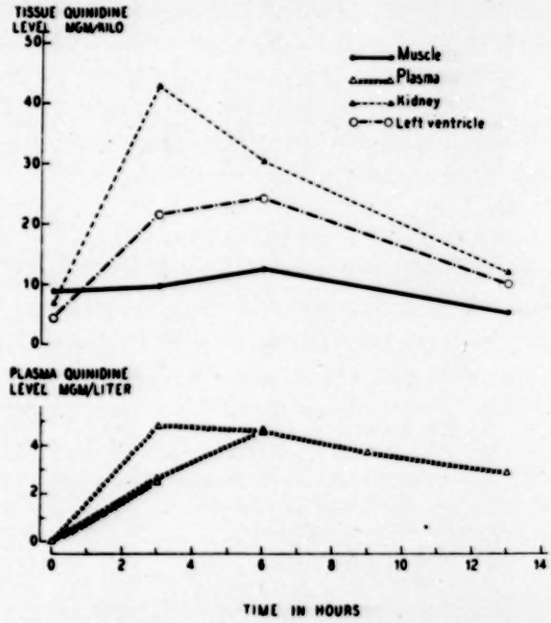


FIG. 5. Venous (four determinations of quinidine plasma levels simultaneously in arterial and venous blood yielded the same results) plasma quinidine level expressed in mg. of the base per liter and quinidine levels expressed in mg. of the base per Kg. in striate muscle, left ventricle and kidney in four dogs at the time they were sacrificed. One dog was used as a control, received no quinidine and was sacrificed at 9 A.M. The other three dogs received 25 mg. quinidine sulfate per Kg. of body weight at 9 A.M. and were sacrificed respectively three, six and thirteen hours after the administration of the drug. In the dog killed six hours after the administration of the drug the plasma quinidine level was also determined three hours after the administration. In the dog sacrificed thirteen hours after the administration of the drug the plasma quinidine level was also determined three, six and nine hours after the administration of the drug.

no quinidine; the other four received in their meat 50 mg. quinidine sulfate per kilo of body weight. The control dog was immediately anesthetized by an intravenous injection of 2 cc/kilo of a 20 per cent solution of sodium barbital. One-half hour after the injection, a sample of arterial blood was drawn from the femoral artery and samples were taken of the striate muscle and kidney. The chest was immediately opened and

samples of left auricle and left ventricle muscle were taken. The time necessary for all samplings ranged from three to seven minutes, generally four or five minutes. The dogs that received their quinidine at 9 A.M. were anesthesized, respectively, at 11:30 A.M., 2:30 P.M., 6:30 P.M. and 10:30 P.M. and were killed at 12 noon, 3 P.M., 7 P.M. and 11 P.M., respectively, i.e., three, six, ten and fourteen hours after the ingestion of quinidine. (Fig. 4 and Table II.)

As 50 mg. of quinidine sulfate per kilo of body weight is a definitely higher dose than the doses previously used in the studies on human beings, a similar experiment with smaller doses of quinidine was performed on a series of five dogs; one dog was again used as a control and received no quinidine whereas the other four received 10 mg. quinidine sulfate per kilo of body weight. The dogs were killed according to the schedule used in the first experiment. The

TABLE II*

Dog No.	Plasma Quinidine (Mg./Liter)	Leg Muscle Quinidine (Mg./Kilo)	Kidney Quinidine (Mg./Kilo)	Left Ventricle Quinidine (Mg./Kilo)	Left Auricle Quinidine (Mg./Kilo)
1. Control	0	1.1	4.4	4.4	4.5
2. Sacrificed 3 hours after drug administration	12.5	60	148.4	148.6	104.1
3. Sacrificed 6 hours after drug administration	5.2	20.7	62.5	31.8	27.2
4. Sacrificed 10 hours after drug administration	3.2	25.3	56.9	45.9	32.9
5. Sacrificed 14 hours after drug administration	2.4	14.8	37.4	23	17.7

* Arterial plasma and tissue quinidine levels (expressed in mg. of the base respectively per liter of plasma and per kilo of tissue) in five dogs. Dog No. 1 was used as a control, received no quinidine and was killed at 9 A.M. Dogs 2, 3, 4 and 5 each received orally 50 mg. quinidine sulfate per kilo of body weight at 9 A.M. and were sacrificed respectively three, six, ten and fourteen hours after the administration of the drug. Blood samples and tissue samples were taken at the time the dogs were sacrificed.

TABLE III*

Dog No.	Plasma Quinidine (Mg./Liter)	Leg Muscle Quinidine (Mg./Kilo)	Kidney Quinidine (Mg./Kilo)	Left Ventricle Quinidine (Mg./Kilo)
1. Control	0	8.9	6.9	4.5
2. Sacrificed 3 hours after drug administration	2.4	9.8	42.8	21.7
3. Sacrificed 6 hours after drug administration				
3 hours after drug administration	4.8			
6 hours after drug administration	4.6	12.6	30.3	24.6
4. Sacrificed 13 hours after drug administration				
3 hours after drug administration	2.5			
6 hours after drug administration	4.6			
9 hours after drug administration	3.7			
13 hours after drug administration	2.9	5.6	12.0	10.3

* Venous plasma and tissue quinidine levels (expressed in mg. of the base, respectively, per liter of plasma and per kilo of tissue) in four dogs. Dog No. 1 was used as a control, received no quinidine and was killed at 9 A.M. Dogs Nos. 2, 3 and 4 each received orally 25 mg. quinidine sulfate per kilo of body weight at 9 A.M. and were killed respectively three, six and thirteen hours after the administration of the drug. Blood samples and tissue samples were taken on all dogs at the time they were sacrificed. Plasma levels were also determined for dog No. 3, three hours after the administration of quinidine and for dog No. 4, three, six and nine hours after the administration of quinidine.

quinidine plasma levels were all very low, i.e., 0.0 mg./liter in the control dog and 0.1, 2.1, 0.5 and 2.8 mg./liter in the dogs fed quinidine and killed three, six, ten and fourteen hours, respectively, after the ingestion of quinidine. The quinidine tissue levels also were very low, in fact not higher in the dogs fed quinidine than in the dogs used as controls in this series as well as in the first series.*

A third experiment was performed on a series of four dogs. One served as a control; the other three were fed 25 mg. quinidine sulfate per kilo and were killed, under anesthesia, three, six and thirteen hours after the administration of the drug. Plasma and tissue quinidine levels (striate muscle, kidney, left ventricle) were determined on samples taken when the dogs were sacrificed. In addition, plasma levels were also determined for the dog killed six hours after the ingestion of quinidine, three hours after the administration of the drug and for the dog killed thirteen hours after the administration of quinidine, three, six and nine hours after the administration of the drug. (Fig. 5 and Table III.)

Results and Discussion. When dogs received 50 mg. quinidine sulfate per kilo, maximal plasma and tissue quinidine concentrations were reached within three hours after the ingestion of the drug. Six hours after the ingestion, there was a sharp decline both in the tissue levels and the plasma level. Ten and fourteen hours after the ingestion, there was a tendency toward a slow decrease in tissue and plasma levels. From the frequency of the determinations we cannot say exactly when the maximal tissue and plasma concentrations occurred or how long they remained maximal but it is obvious that the plasma level was high enough, long enough, so that a much higher level was obtained in the leg muscle, kidney, left ventricle and auricle. If we compare Figure 5 with any one of the studies depicted in Figure 1, study 6 W. H. for example (being fully aware that one study is on a human being and the other one an experiment on a dog, and also that at least the plasma level curves in both types of study are comparable in their general outline) we will see that six hours after the ingestion, (1) there has been a definite decrease of the plasma level in both the patient and the dog and (2) the tissue level has fallen markedly but the intensity of the effect on the circus rate has decreased very little. It seems, therefore, that the first two explanations offered to account for the discrepancies between quinidine plasma level and intensity of its effect on the circus rate are untenable. It can be concluded that whereas tissues fix some quinidine at low plasma concentrations, they do not become saturated with relatively low plasma levels and also that the time during which the auricles were exposed to a high plasma level was long enough for them to fix an enormous quantity of quinidine. It seems, therefore, that the reason why the intensity of the cardiac effect is not more marked early in the period of action of quinidine is that, with any increment of the quinidine auricular level, there is a decrease in the increment of the cardiac effect which tends toward zero with any further increment in the quinidine auricular level. Whether later in the period of action of quinidine, the plasma level is comparatively lower than the auricular level, seems to be improbable as there is no obvious difference in the rate of disappearance of quinidine from the plasma and from the tissues.

An analysis of experiments in which dogs received 25 mg. quinidine sulfate per kilo (Figure 5, Table III) yields essentially the same conclusions. No auricular tissue level was determined in this experiment because of the parallelism noted in the first series of dogs between auricular and ventricular levels.

* With the method used to determine quinidine tissue levels, the tissues of the control dogs were found to contain slight amounts of some material indistinguishable from quinidine.

SUMMARY AND CONCLUSIONS

An attempt was made to correlate the concentration of quinidine in the plasma,

the concentration of quinidine in the heart (auricles and ventricles) and the intensity of the effect of quinidine on the heart.

1. The first problem consisted of studying, in human beings, the correlation between the plasma concentration of quinidine and the intensity of the effect of quinidine on the heart as measured by the changes of the rate of the circus movement in auricular fibrillation. Patients with chronic auricular fibrillation were given orally single and/or repeated doses of quinidine sulfate. The concentration of the drug in the plasma and the intensity of its effect on the rate of the circus movement were followed.

In seven studies in which one single dose of from 0.4 to 0.8 Gm. of quinidine sulfate was given, the intensity of the cardiac effect of the drug and its plasma concentration were found to be grossly parallel but not parallel in a strictly quantitative manner. Indeed, discrepancies between intensity of cardiac effect and quinidine plasma concentration were found, the plasma level of the drug decreasing faster than the intensity of its cardiac effect.

In three studies in which repeated doses (0.4 Gm. every two hours for three or four doses) of quinidine sulfate were given, there seemed to be more parallelism between plasma concentration and intensity of the cardiac effect. This may be more apparent than real because the patients were not followed long enough.

The main possibilities among several theoretical explanations that may explain the discrepancies observed between quinidine plasma concentration and intensity of the cardiac effect were discussed.

2. The second problem consisted in an attempt to correlate in dogs the concentration of quinidine in the plasma and in the heart muscle. Such experiments showed that the concentration of quinidine in the tissues is much higher than the plasma concentration of the drug. The time at which the highest tissue concentration is reached corresponds with the peak of the plasma concentration. Following the rise there is a rather sudden drop in tissue and plasma concentrations, then a more gradual decrease.

3. If the results observed in the experiments on dogs are applicable to human beings, it would appear that the main factor accounting for the discrepancies observed between quinidine plasma concentration and intensity of the effect on the heart is the fact that the cardiac effect is not proportional to either the plasma or myocardial concentration of the drug. Indeed, any further increase in the heart concentration yields a diminished increment of cardiac effect.

We want to express our gratitude to Dr. David P. Earle and his collaborators at the Goldwater Memorial Hospital, Welfare Hospital, New York City, for their help in doing the quinidine determinations.

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Clinical Evaluation of the Treatment of Pneumococcic Type III Pneumonia*

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THE bacteriologic and clinical characteristics which distinguish type III pneumococcus from other pneumococcic types causing pneumonia are well known. From a practical viewpoint the chief problem confronting the internist has been the resistance of this type of pneumonia to treatment. Type III pneumonia warrants special study, not only because it carries the highest case fatality rate for pneumococcic pneumonia, but because it is one of the most frequent forms of pneumonia. (Table I.)

This study presents comparative results in the treatment of pneumococcus type III pneumonia with various combinations of type-specific antiserum, sulfadiazine and penicillin.

During a three-year period (1942 to 1945), 2,176 consecutive patients with pneumococcic pneumonia were treated at the Permanente Foundation Hospital. The diagnosis of pneumonia was substantiated in every patient by indisputable physical findings or a positive roentgenogram. Patients with pneumonia as a secondary diagnosis to another disease were excluded. Sputum examination in every patient showed the predominant organism to be pneumococcus. Specific typing by the Neufeld method was obtainable in 70 per cent of the patients.

As a cause of pneumonia in this series, the type III pneumococcus was found to be the fourth most frequent etiological organism. (Table I.) In a nationwide survey of the bacterial etiology of pneumonia from 1938 to 1940, Rumreich[1] found type III to be one of the first four most frequent causes of pneumococcic pneumonia in each of the six representative states studied. (Table II.) Of 16,813 patients with pneumonia compiled by Heffron,[2] 10.8 per cent were due to this organism.

TABLE I
LEADING PNEUMOCOCCIC TYPES AS CAUSES OF DEATH FROM PNEUMONIA, 1942–1945

Pneumococcus Type	No. Cases	No. Deaths	Per Cent Mortality
III	103	21	20.4
II	61	9	14.8
VII	241	31	12.8
IV	106	11	10.4
I	152	81	7.2
XII	79	5	6.3
V	91	5	5.5
XXV	124	5	4.0
All others*	2,073	105	5.1
All cases	2,176	126	5.8

* All cases exclusive of Type III.

Among the clinical features which contribute to the high mortality rate for pneumococcus type III pneumonia is its greater incidence among older age groups. This is clearly demonstrated in Table III which shows that over half (51.4 per cent) of all patients with type III pneumonia were over the age of fifty, whereas only about one-fourth (26.8 per cent) of all other types of pneumonia occurred in patients of this older age group. Likewise, only 11.6 per

* From the Department of Medicine, Permanente Foundation Hospital, Oakland, Calif. Statistics compiled by Martha Eaton, A.B. and Margaret Chamberlin.

TABLE II

COMPARATIVE INCIDENCE OF TYPE III PNEUMOCOCCIC PNEUMONIA IN SIX REPRESENTATIVE STATES (1938–1940)*

California		Colorado		Illinois		Louisiana		Missouri		New Jersey	
Type	Per Cent	Type	Per Cent	Type	Per Cent	Type	Per Cent	Type	Per Cent	Type	Per Cent
III	13.26	I	16.08	I	19.40	I	22.19	I	18.95	I	20.28
I	11.10	II	15.25	III	13.61	VII	10.64	III	13.68	III	13.94
VII	9.84	III	12.45	II	10.15	>XXXIII	7.02	VIII	8.79	VIII	9.12
VIII	7.19	VII	8.08	VII	8.27	III	6.72	VII	6.32	VII	7.50

* From Rumreich.[1]

TABLE III

COMPARATIVE INCIDENCE AND MORTALITY BY AGE

Age (Years)	Type III				All Other Types			
	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality
10–19	3	2.9	0	0	121	5.8	1	0.8
20–29	9	8.7	1	6.3	400	19.3	7	1.7
30–39	15	14.6	5	22.7	508	24.6	11	2.2
40–49	23	21.4	9	45.0	488	23.5	31	6.3
50–59	27	26.2	5	31.3	336	16.2	34	10.1
Over 60	26	25.2	1	11.1	220	10.6	21	9.6
Total	103	100.0	21	20.4	2,073	100.0	105	5.1

TABLE IV

COMPARATIVE INCIDENCE AND MORTALITY BY AGE GROUPS, EXCLUDING ASSOCIATED DISEASES

Age (Years)	Type III				All Other Types			
	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality
10–30	7	9.0	0	0	411	26.1	7	1.7
30–49	27	34.6	13	48.2	790	50.0	28	3.5
50–70	44	56.4	5	11.4	373	27.6	29	7.8
Total	78	100.0	18	23.1	1,574	100.0	64	4.1

cent of patients with pneumococcus type III pneumonia were under the age of thirty, whereas 25.1 per cent of patients with pneumonia due to other pneumococcic types were in the younger age group. Other studies have found the proportion of patients with type III pneumonia over the age of forty to be 60 per cent,[3] 69 per cent[4] and 81 per cent,[5] as compared to 73 per cent in this series. (Table III.) That this is an important factor in producing the higher gross mortality rates for this series of type III pneumonia is obvious, as the average mortality rate for a group of patients over the age of fifty with pneumococcic pneumonia is several times that for a group under the age of thirty. (Table III.) However, it is apparent from Table III that for each decade the average patient fatality rate for type III pneumonia tended to be higher than that for pneumonia due to other types. This suggests an increased virulence of the organism itself since groups of patients of the same age are compared.

Since the increased fatality rate in older patients might be attributed to the greater frequency of serious associated diseases, Table IV presents comparative mortality rates for this series of patients, excluding all patients with associated diseases. About 24 per cent of patients with type II pneumonia and 20 per cent of patients with other types of pneumococcic pneumonia had concomitant conditions.

It is apparent from Table IV that adults with simple uncomplicated pneumococcic pneumonia of any type under the age of thirty have a very low mortality rate. Cecil[3] emphasized that even before chemotherapy the mortality was low in those patients with type III pneumonia under the age of thirty. However, patients with type III pneumonia

TABLE V

COMPARATIVE INCIDENCE AND MORTALITY BY NUMBER OF PNEUMOCOCCI PER OIL FIELD, BLOOD CULTURE, NUMBER OF LOBES INVOLVED AND LEUKOCYTE COUNT

	Type III				All Other Types			
	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality
Sputum Pneumo Count*								
Under 10	13	14.3	1	7.7	481	30.8	2	0.4
11–30	33	36.3	1	3.0	514	32.9	9	1.7
31–74	23	25.3	8	34.8	394	25.2	20	5.1
Over 75	22	24.1	9	40.9	176	11.3	27	15.3
Blood Culture								
Positive	8	7.8	4	57.1	204	9.9	36	17.6
Negative	80	77.6	11	13.7	1,597	77.0	38	2.4
Unknown	15	14.6	6	....	272	13.1	31	
Lobe Involvement								
Single	68	66.0	10	14.7	1,488	71.8	32	2.2
Multiple	35	34.0	11	31.4	585	28.2	73	12.5
Leukocyte Count								
Under 6,000	12	11.7	10	83.3	76	3.7	31	40.8
6,000–10,000	14	13.6	3	21.4	233	11.2	25	10.7
10,000–25,000	57	55.3	5	8.8	1,105	53.3	25	3.2
Over 25,000	19	18.4	2	12.5	646	31.1	10	1.5
Unknown	1	1.0	1	....	13	.....	4	
All Cases	103	100.0	21	20.4	2,073	100.0	105	5.1

* Data available in only 1,656 cases.

between the ages of thirty and fifty have an unusually high mortality rate even in the absence of associated diseases. In elderly patients (over the age of fifty), it is suggested that any increase in the fatality rate of type III over pneumococcic pneumonia may very well be due to associated diseases, since in the absence of concomitant conditions the mortality rates for this age group were not remarkably dissimilar.

To compare further the severity of the illness in patients with type III pneumonia and pneumococcic pneumonia due to other types, Table V presents data concerning certain important factors influencing prognosis and mortality in pneumonia. The number of organisms in the sputum is an important index of the severity of the infection. Although the reliability of the sputum pneumococci count for type III pneumonia has been questioned,[6] Table V shows a correlation between an increasing pneumococci count and mortality. Whether the sputum showed few or many organisms for each group so classified, patients with type III pneumonia had higher mortality rates than those with pneumonia due to other pneumococcic types. There was also a greater frequency of patients with large numbers of organisms in their sputum among the type III pneumonias than among other types of pneumonia.

Patients with pneumonia without demonstrable bacteremia had much higher mortality rates for the type III than for other pneumococcic types. (Table V.) Although the incidence of bacteremia was apparently the same in both groups, patients with type

TABLE VI

COMPARATIVE INCIDENCE AND MORTALITY BY SEX

	Type III				All Other Types			
	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality
Male	95	92.2	19	20.0	1,768	85.3	97	5.5
Female	8	7.8	2	25.0	305	14.7	8	2.6
Total	103	100.0	21	20.4	2,073	100.0	105	5.0

TABLE VII

COMPARATIVE INCIDENCE AND MORTALITY BY DAYS ILL BEFORE ADMISSION

No. Days	Type III				All Other Types			
	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality	No. Cases	Per Cent Incidence	No. Deaths	Per Cent Mortality
1	31	20.4	1	5.9	547	26.4	16	2.9
2	17	16.5	2	11.8	396	19.1	16	4.0
3–4	29	28.2	7	24.1	513	24.7	25	4.9
Over 4	34	33.0	10	29.4	555	26.8	37	6.7
Unknown	2	1.9	1	....	62	3.0	11	
Total	103	100.0	21	20.4	2,073	100.0	105	5.1

III pneumonia and bacteremia showed over three times the fatality rate for that of other pneumococcic types. The extent of pneumonia is an important factor influencing mortality and Table V shows that multiple lobe involvement was approximately as frequent in both groups of patients. For either single or multiple lobe involvement patients with type III pneumonia had a much higher fatality rate than those with pneumonia due to other types. Leukopenia is a grave prognostic sign in pneumococcic pneumonia. Table V shows that severe leukopenia (under 6,000 cells per cu. mm.) was three times more frequent in type III pneumonia and had an associated mortality rate of about twice that for pneumococcic pneumonia due to other types. In general, Table V demonstrates that when classified in groups according to similar severity factors, type III pneumonia consistently shows a higher mortality rate than pneumococcic pneumonia due to other types.

That the incidence of pneumococcic pneumonia is greater among males is well recognized; however, Table VI reveals that this difference was even more marked for type III. For either sex, however, the mortality rate was higher for type III than for pneumonia due to other types. The higher incidence of type III pneumonia in females as reported by Cecil[3] was not found in this series.

The interval between the onset of pneumonia and the time of admission to the hospital is an important factor influencing mortality. Table VII shows that this was even more striking for type III pneumonia in which the mortality rate for patients who had been ill for three or more days prior to admission was at least four times that of those admitted in the first or second day of illness. By each day of illness at the time of admission the mortality rate for type III pneumonia was higher than that for pneumonia due to other types.

It is further evident from Table VIII that patients with type III pneumonia had a tendency to require a slightly longer period of hospitalization for recovery. However, other than a possibly greater frequency of lung abscesses the incidence of common complicating conditions was similar to that found in pneumococcic pneumonia due to other types. (Table IX.)

TABLE VIII
COMPARATIVE LENGTH OF HOSPITAL STAY (EXCLUSIVE OF DEATHS)

	Type III		All Other Types	
	No. Cases	Per Cent Incidence	No. Cases	Per Cent Incidence
<7 days	43	52.5	1,219	61.8
7–14	23	28.0	565	28.9
15–21	8	9.8	88	4.5
22–28	2	2.4	42	2.1
>28	6	7.3	54	2.7
Total	82	100.0	1,968	100.0

TABLE IX
COMPARATIVE INCIDENCE OF CERTAIN COMPLICATING CONDITIONS

	Type III		All Other Types	
	No. Cases	Per Cent Incidence	No. Cases	Per Cent Incidence
Sterile effusions	6	5.7	94	4.1
Empyema	0	0.0	4	0.2
Lung abscess	2	1.9	7	0.3
Endocarditis	0	0.0	3	0.1
Meningitis	0	0.0	2	0.1

EVALUATION OF TREATMENT

During the first half of this study, which was prior to the advent of penicillin, patients with pneumococcic pneumonia were treated with sulfadiazine and adjuvant type-specific antiserum when indicated.

Type III pneumococcic antiserum in large doses was used in thirty-three of forty-eight patients (56 per cent). This group of patients was also treated with two different dosage regimens of sulfadiazine, as reported elsewhere.[7] One group was treated with usual doses of sulfadiazine (8 Gm. daily, maintaining average blood levels of 8 to 10 mg. per 100 cu. cm.) and a second group, demonstrated to be of comparable severity, was treated with double these doses (maintaining blood levels of 12 to 20 mg.). It was shown that a general decrease in the mortality rate occurred in all types of pneumococcic pneumonia receiving the double dose, *exclusive* of type III. (Table x.) It was also pointed out that the group of patients with type III pneumonia receiving double doses of sulfadiazine also had received type III antiserum in 14 per cent more instances than those with usual doses. As is indicated in Table x the increased use of serum and /or the increased dosage of sulfadiazine were ineffectual in reducing the mortality of type III pneumococcus pneumonia. In the group of forty-seven patients with type III pneumonia, who received very large doses of sulfadiazine and in whom the majority also received large doses of serum, the fatality rate was maintained at the exceedingly high rate of 34 per cent.

With the advent of penicillin a second group of patients with pneumococcic pneumonia, demonstrated to be of comparable severity, were treated with sulfadiazine and penicillin.[8] Of forty-six patients with type III pneumonia in this group, twenty-seven (58 per cent) were classified as being seriously ill and were treated with both penicillin and sulfadiazine with a resultant mortality rate of 7.4 per cent. (Patients similarly classified and treated with both specific antiserum and sulfadiazine had a mortality rate of 50.0 per cent). The gross mortality rate for patients with type III pneumonia treated with sulfadiazine and adjuvant penicillin was 4.3 per cent. (Table x.) Penicillin was administered most frequently in doses of 25,000 units intramuscularly every three hours. Severely ill patients received 40,000 units intramuscularly every three hours or 10,000 units per hour by continuous intravenous drip. Penicillin therapy was usually continued until

TABLE X

COMPARATIVE MORTALITY RATES BY METHOD OF TREATMENT

Pneumococcus Type	Sulfadiazine with Adjuvant Serum Therapy						Sulfadiazine with Adjuvant Penicillin Therapy		
	Usual Dose Sulfadiazine			Double Dose Sulfadiazine					
	No. Patients	No. Deaths	Per Cent Mortality	No. Patients	No. Deaths	Per Cent Mortality	No. Patients	No. Deaths	Per Cent Mortality
III	11	2	18.2	47	16	34.0	46	2	4.3
II	22	6	27.3	10	2	20.0	29	1	3.4
VII	68	20	29.4	92	10	10.9	81	1	1.3
IV	34	5	14.7	31	4	12.9	41	2	4.2
I	29	4	13.8	52	6	11.5	71	1	1.4
XII	14	2	14.3	30	2	6.7	35	1	2.9
V	11	2	18.2	45	2	4.4	35	1	2.9
XXV	26	3	11.5	55	1	1.8	43	1	2.4

the patient was afebrile at least forty-eight hours. Other details of treatment of these patients have been outlined elsewhere.[9]

SUMMARY AND CONCLUSIONS

In a series of 2,176 consecutive patients with pneumococcic pneumonia, type III was one of the most frequent forms and carried the highest mortality rate. When compared in groups according to similar severity factors, type III pneumonia constantly showed a higher subject fatality rate than that for pneumococcic pneumonia due to other types. Penicillin was the most effective agent in the treatment of pneumococcic type III pneumonia. Sulfadiazine and type III antiserum were relatively ineffectual in any dosage against this type of pneumonia.

Patients with pneumococcic type III pneumonia classified as severely ill who were treated with large doses of both specific antiserum and sulfadiazine had a gross fatality rate of 50 per cent. Patients similarly classified and treated with penicillin and sulfadiazine had a mortality rate of only 7.4 per cent. In this series the gross mortality rate for type III pneumococcic pneumonia prior to the advent of penicillin was 29.3 per cent; with penicillin therapy the mortality rate was 4.3 per cent.

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Review

Mechanisms of Action of Serum Albumin Therapy in Internal Medicine*

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In the last two decades accumulating evidence has cast doubt on the concept (familiar as Starling's hypothesis) that the volume of extracellular extravascular fluid is determined by the balance of capillary hydrostatic filtration pressure against osmotic pressure of plasma proteins and tissue pressure.

The nephrotic syndrome provided an early source of this doubt in the finding that spontaneous diuresis is initiated and edema begins to disappear with no change in the level of plasma proteins.[1,2] More recently, in cirrhotic patients, identical total protein and albumin levels in the presence and following disappearance of ascites have been reported.[3,4] Again, normal protein levels noted by groups studying nutritional edema due to war starvation have been supplemented by findings by Ancel Keys and coworkers in nutritional edema experimentally produced.[5] Unaware of Govaerts' extensive direct measurements of osmotic pressures in famine edema far lower than expected from Howe serum albumin determinations,[6,7] Keys has interpreted the apparent lack of balance of calculated osmotic and filtration pressure to suggest that an occasionally disturbed equilibrium is not a suitable concept for the relation of intravascular to extravascular water.

The technics underlying most of the older experimental evidence relating plasma proteins to water balance have had the common aim of lowering osmotic pressure. Human albumin in large quantities has recently, and for the first time,[8] permitted the controlled upward variation within wide limits of the osmotic properties of plasma by the substance chiefly responsible for it in the normal state.[9] This albumin, together with other fractions of plasma of different chemical and biologic properties, is now becoming available to investigators through a national blood collection and fractionation program under the American Red Cross. This presentation undertakes to review the evidence that has emerged in this clinic on the subject of mechanisms and clinical indications in civilian practice in the light of findings in other clinics and to suggest avenues for further investigation.

CIRRHOSIS OF THE LIVER

Spontaneous variability of water balance in the chronic diseases of the kidney and liver necessitates extremely careful selection and prolonged observation of patients before and after therapy to insure validity of correlations between therapy and measurable changes and to prevent waste of valuable material in uninterpretable clinical situations.

The arrest of cirrhotic ascites, first recorded in the early studies of Janeway and co-workers,[10] was interpreted correctly with great caution. Subsequently, Gibson, in the course of testing large quantities of albumin

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for the Navy, encountered further instances of ascitic arrest.[11]

In the past year Dr. Kendall Emerson and the author have subjected this phenomenon to detailed analysis in two patients suffering from severe stabilized hepatic cirrhosis who, over protracted periods of observation, failed to show serum albumin increases on nutritional therapy. This type of patient was chosen because Patek and Post[12] have shown that such a failure of albumin response indicates hepatic damage of gravest prognosis.

Using an initial total dose usually over 700 Gm. of albumin at a rate over 50 Gm. per day, the time required to stop ascites formation (approximately two weeks) is far lower than has been observed with other therapies. (For the most recent of these, "Rockefeller liver," Hoagland[4] and his colleagues have reported times varying between six months and a year.)

Measurements of the effective serum osmotic pressure* (i.e., the pressure developed by serum against the protein-containing ascitic fluid simultaneously obtained) have indicated that when this variable is above a critical level (differing in various patients) ascitic formation ceases; when below this critical level, ascitic formation resumes.

Rates of ascitic formation have been determined by repeated taps carried out on a full but not distended abdomen. Distention, by influencing hydrostatic pressure in the peritoneal cavity can, in turn, influence formation rates. Thus, our findings in cirrhosis do not pertain to any diuretic effect of intravenous albumin but rather to its effect in prevention of ascites. Such ascitic fluid as formed before or during therapy has always been removed by a needle, not through renal water excretion.

In Gibson's studies[11] the water was not emptied by paracentesis before therapy. In his successful cases the water removed from the abdominal cavity was presumably excreted by the kidneys. The periods required for ascitic arrest were somewhat longer than in our series of patients.

The evidence thus far accumulated does not mean that albumin will be effective in every cirrhotic patient. It is quite conceivable that in an occasional patient with severe mechanical obstruction to portal flow (increased portal capillary permeability), an induced rise in serum albumin will be exactly balanced by a rise in ascitic fluid albumin, the effective osmotic pressure will not change and the ascites will remain. Janeway[13] observed a patient with childhood cirrhosis in whom, on albumin therapy in the absence of taps, ascitic fluid protein rose as high as 6 Gm. per cent. Patek[14] likewise observed exactly parallel rises in serum and ascitic fluid osmotic pressures following albumin dosage somewhat less in amount than was employed in our own studies.

However, before a patient is deemed unamenable to albumin, therapy should be carried out with the patient tapped dry for the following reason: Water removal without simultaneous protein removal from the peritoneal cavity yields a concentration of ascitic protein and thus, for given plasma osmotic pressure, a decreased effective pressure. When both ascitic water and ascitic protein are removed together through a trochar, this cannot occur. We have recently observed extremely slow disappearance of ascites on albumin therapy from an ascites-loaded patient in whom, without immediate change in serum osmotic pressure, no fluid reformed after tapping was performed.

Maintenance dose, estimated from rates of decline of serum osmotic pressure, will vary according to the severity of the disease between 20 Gm. a week for a patient with severe cirrhosis to 100 Gm. a week for a patient with terminal cirrhosis. Administration can be carried out easily at weekly or greater intervals in the office or clinic.

There is as yet no reliable evidence that albumin influences any manifestations of cirrhosis other than water balance. Control of ascites has been achieved in hepatic

* We are indebted to Professor George Scatchard, Research Laboratory of Physical Chemistry, Massachusetts Institute of Technology, for making available the facilities with which we have carried out these measurements.

coma without the slightest apparent effect on the coma. Furthermore, albumin is no substitute for nutritional therapy which in past years has given the first advance in prognosis of some patients with cirrhosis. Indeed, it is to be hoped, from Hoagland's[4] recent studies, that in many cases intensive nutritional therapy may permit resumption of spontaneous albumin formation by the patient and thus discontinuance of parenteral albumin within a year or so after initial decompensation. The chief value of albumin in cirrhosis will probably lie in its capacity to rid promptly the patient with early decompensated cirrhosis of the heavy disabilities of being water-logged.

IDIOPATHIC HYPOPROTEINEMIA

There is a small, ill defined group of patients who, despite lack of evidence of renal or hepatic disease, present edema and low plasma protein levels quite intractable to administration of high protein diets. The mechanism of this disorder, not as yet elucidated experimentally, has been ascribed to defects in protein absorption or synthesis.[15–20]

Patients of this type, whom we have studied at the Peter Bent Brigham Hospital in the last five years,[21] have had in common plasma protein electrophoretic schlieren diagrams reminiscent, in low albumin and gamma globulin components,* of the diagrams characteristic of the nephrotic syndrome; resemblance to nephrosis extends to low urine sodium outputs,† edema fluid proteins below 0.25 per cent (chiefly albumin on electrophoresis) and normal liver function tests; there has however been no significant albuminuria.

The response of two of these patients to intravenous salt-poor albumin has been strikingly different. In one whose moderate edema was of three years' standing, 250 Gm. over five days yielded a sustained rise of serum osmotic pressure from an initial 125 mm. H_2O to 415 mm. H_2O (normal 375 mm. H_2O) and diuresis of sodium and water with complete loss of edema. The protein level of the last visible edema fluid was below 1 Gm. per cent. Therapy in this amount served to maintain the patient edema-free for over two months. A comparable quantity of albumin immediately removed the first traces of reaccumulating edema at the end of this time.

Another patient, incapacitated by enormous anasarca which for two years had failed to respond to nearly all known diuretic regimens, experienced her first diuresis (15 Kg. weight loss) in a thirty-day period during which 750 Gm. of salt-poor albumin were administered.

At the end of this period, despite continued albumin, her weight curve flattened, her sodium output (which had risen from a base line of under 1 mEq. to over 150 mEq. a day in the first week of therapy) declined. It was apparent that the albumin had lost its initial diuretic effect. At this time it was found that the protein content of the edema fluid had increased tenfold to 3 Gm. per cent (almost pure albumin by electrophoresis). Nearly all the administered albumin could thus be accounted for.

By consequence, although the absolute serum osmotic pressure (measured against saline) had greatly increased during therapy, the effective serum osmotic pressure (measured against edema fluid) actually decreased which was a direction of change exactly opposite to that encountered in treating cirrhosis. Moreover, at the beginning of the therapy period, sudden introduction of 50 Gm. albumin into the circulation yielded an increase in plasma volume sufficient to maintain an almost unchanged osmotic pressure; at the end of the therapy period the same dose resulted in a rise of osmotic pressure without significant increase in plasma volume.* That the first type of re-

* In cirrhosis of the liver the gamma globulin component is usually elevated.

† We are indebted to Dr. William Wallace of the Children's Hospital for his generous collaboration in the many sodium analyses made in this study which have been possible through the flame photometer of his construction.

* The following hypothesis is suggested for the mechanism of these two types of response: Iso-osmotic addition of albumin occurs when the plasma osmotic and mean filtration pressure are almost balanced, such that a

sponse (iso-osmotic addition of albumin) was almost uniformly followed by diuresis of sodium and water and that the second type (isometric addition of albumin) was almost never followed in a like manner, suggests that the diuretic action of albumin in the hypoproteinemic state is related to sustained plasma volume increase.* Studies made on a patient with constrictive pericarditis, next to be considered, further suggest that such an increase is a necessary but not sufficient condition for diuresis. These suggestions will be carried through our consideration of the mechanism of action in the nephrotic syndrome.

The findings in these two patients indicate that "idiopathic hypoproteinemia" can be subdivided into at least two syndromes, perhaps unrelated. In the first, capillary permeability to albumin is not deranged, effective serum osmotic pressure may be brought to normal and disability consequent to edema entirely obviated by intravenous albumin in reasonable dosage. In the second, the primary effect is an increased permeability of peripheral capillaries to albumin.† Short of correction of this defect, effective therapy will probably require a range of molecular weights far greater than albumin (69,000) to avoid protein loss into interstitial fluid and to raise effective plasma osmotic pressure.

CONSTRICTIVE PERICARDITIS

An almost constant feature of the syndrome of constrictive pericarditis is hypoalbuminemia. This is generally believed to augment the effect of high venous pressure in producing chronic edema. In general, a high protein diet in the preoperative state has had very little effect on protein level; in the postoperative state (if the operation has been successful) response to diet is usually very slow.

Intravenous administration of large quantities of albumin in one patient has permitted analysis of the interaction of plasma osmotic pressure and plasma volume and venous pressure in the pathogenesis of edema in various stages of this syndrome.*

Preoperatively, the patient's plasma osmotic pressure was about one-half and the venous pressure somewhat over twice the respective normal values for these variables. The restoration of osmotic pressure to normal by some 600 Gm. albumin in three weeks was paralleled by a striking rise in venous pressure and blood volume. There was, however, no weight loss; no urinary diuresis of sodium or water. There was no leakage of albumin into the edema fluid, in contrast to the situation in one type of idiopathic hypoproteinemia. At the end of the preoperative period of albumin therapy response to sudden addition of 50 Gm. of albumin was essentially isometric; the consequent rise in osmotic pressure of the serum was almost precisely balanced by a rise in venous pressure; there was little further increase in plasma volume and analysis of multiple, four-hourly urine specimens showed no transient increase in sodium output.

small further increase in osmotic pressure is enough to shift water immediately out of the interstitial compartment; isometric addition occurs when plasma osmotic pressure is already lower than mean filtration pressure and filtration out of the blood stream is in point of fact taking place (as shown by increasing edema); in this instance a considerable rise in osmotic pressure is required before equilibrium is reached and passed, such that reversal of flow, with consequent increase in plasma volume, can occur.

The chief obstacle in the precise verification of this hypothesis is the difficulty in experimentally determining a significant figure for *mean tissue pressure*. This variable, which assumes great significance in the Warren-Stead hypothesis[32] of cardiac decompensation edema, has been perhaps most reliably estimated locally by Landis[33] in acute experiments and by indirect means. The use of Landis' quantitative relationship between acutely produced edema and tissue pressure is almost certainly invalid in treating chronic edema.

A second variable impossible of precise measurement in human disease is rate of lymph flow, the effect of which will be to remove fluid from a region into which filtration is taking place.

* That this diuresis is not related to rate of change of plasma volume has been shown in producing equivalent shifts, both in size and speed but not in duration, by glucose *without* diuresis of salt and water.

† Dr. Irving Simons of New York has extensive unpublished studies on another instance of this phenomenon.[34]

* We are indebted to Dr. Eugene Eppinger and Dr. Robert Gross for their advice and collaboration in the study of this patient.

In the first three postoperative weeks plasma osmotic pressure fell to less than two-thirds of normal. Response to a sudden injection of 50 Gm. albumin differed from the preoperative response chiefly in venous pressures under 125 mm. saline; although plasma volume increased somewhat with the induced, rapid rise of osmotic pressure to five-fourths normal, no transient diuresis of salt or water was observed. However, after administration of some 300 additional Gm. of albumin in six days, for the first time in the patient's course urinary sodium output rose above the previous extraordinarily low maximum of 3 mEq. a day. After 300 more Gm. a daily output of over 50 mEq. was attained. The sodium output continued to approach the normal for the patient's intake after normal osmotic pressure was reached and albumin stopped.

Eppinger and Burwell[25] have recently shown a considerable lag between successful pericardectomy and recovery of ability to increase cardiac output in response to stress which constitutes the fundamental physiologic abnormality of the syndrome.[26] The findings in the patient herein studied provide strong clinical suggestion that an increase in blood volume induced by albumin cannot set off renal diuresis of salt and water without an increase in cardiac output which may in turn lead to an increased renal blood flow. Whereas our group has not been set up to carry out direct simultaneous measurements of these variables by the cardiac catheter and modern renal clearance methods, such measurements are now clearly indicated to define the relation of these variables and others perhaps now unknown in the diuresis following albumin.

From the standpoint of therapy this patient's case corroborates a similar experience of Janeway and his colleagues in the suggestion that albumin (however conducive to wound healing) will not remove edema preoperatively. Once the fundamental circulatory defect has been obviated by operation, albumin becomes a valuable therapeutic adjunct in permitting restoration of plasma osmotic pressure to normal far more rapidly than is possible by diet alone and will thus give the patient the fastest edema removal consistent with his circulatory status.

EDEMA OF CARDIAC DECOMPENSATION

Albumin therapy in cardiac decompensation of other than mechanical origin is complicated by the risk of pulmonary edema attending further increase of the already abnormally large blood volume. Moreover, the inability of the kidney in ordinary decompensation to excrete sodium is strongly reminiscent of the behavior of the structurally undiseased kidney in constrictive pericarditis; Warren-Stead hypothesis[22] puts these functional abnormalities on the common basis of fixed, low cardiac output. It is thus possible that an increase in plasma volume as a result of albumin may, in the presence of a failing myocardium, simply result in a concomitant rise in venous pressure without diuresis of salt and water. While cautious exploration is in progress with phlebotomy sets in readiness for pulmonary edema, I think that none of our group is as yet ready to specify indications for salt-poor albumin in edema of ordinary cardiac decompensation.

EDEMA OF MALNUTRITION

Whereas we have not had opportunity to study edema of the famine type, we have been able, with a total dosage somewhat less than required in cirrhosis (about 500 Gm.), to remove edema completely from two patients with profound hypoproteinemia due to malignancy. The benefit, although purely symptomatic, has been striking, notably in the presence of cerebral metastasis.

The rapid restoration of plasma osmotic pressure possible by concentrated albumin in such dosage has greatest therapeutic implications in the preparation of nutritionally hypoproteinemic patients for surgery.

NEPHROTIC SYNDROME

The effectiveness of albumin in cirrhosis, as contrasted with the permeable type of hypoproteinemia, is based on the fact that at

least one-sixth of the material administered remains in the circulation to perform osmotic work. Recent studies by Dr. Emerson and myself have served to confirm the earlier experience of this clinic on albumin in the adult (glomerulonephritic) nephrotic state,[27] namely, that administration of 25 to 50 Gm. a day usually yields a daily loss between .25 and .50 Kg. of edema with a corresponding increase in the sodium output of the urine. In contrast to cirrhosis, when salt restriction is not necessary, effectiveness in the nephrotic state usually requires rigid restriction of dietary sodium and the use of salt-poor albumin. After the first two or three days of therapy, however, excessive albuminuria balances almost all the albumin administered. After as much as thirty days of therapy, although the plasma albumin may be slightly increased, the serum osmotic pressure remains under one-half the normal value. Dr. Emerson and I have recently encountered instances when urinary excretion of parenteral albumin is quantitative from the very beginning; in such instances, no diuresis whatever accompanied therapy.

We have seen no evidence of shift in the underlying status of the disease. Following therapy, the plasma albumin level has usually dropped and edema, sooner or later, has re-accumulated. (This experience is in accord with the recent studies of Hutchins, Janeway and their colleagues at The Children's Hospital.) Moreover, in two adults whose glomerulonephritis, although still characterized by nephrotic edema, had progressed to considerable impairment of renal function, intractable uremia followed within a month of albumin therapy. Further experience will be required to determine whether this eventuality is outside the expected incidence in the natural history of the disease. The effect of albumin on renal function is now under examination here and at other clinics.

From the standpoint of mechanism, comparison of the dynamics of spontaneous nephrotic diuresis with the dynamics of diuresis following albumin administration gives best plausibility to the following modified version of the old view, that the forces governing the accumulation of nephrotic edema relate chiefly to the lowered colloid osmotic pressure of the serum which in turn is due chiefly to renal loss of albumin.

Just as in the initiation of spontaneous diuresis, the diuresis following an initial injection of salt-poor albumin in the nephrotic state (except for a very slight initial rise) proceeds without much change in osmotic pressure.[28,29] On daily repeated injections a rise in average plasma volume occurs of a magnitude quite comparable to that observed by MacArthur[30] in nephrosis during prolonged spontaneous diuresis.

This suggests the following mechanism of spontaneous diuresis: The initiating factor is a decrease of renal permeability to albumin which, in the presence of a constant production rate, leads to an essentially iso-osmotic addition of albumin to the circulation, comparable to that encountered in an albumin injection by vein. That minimal changes in osmotic pressure can effect large transports of water is not surprising from the point of view of equilibrium relations. An analogy replacing chemical potential by gravitational potential is as follows: although water will only run downhill, it takes a very little hill to effect the transport of a large amount of water, presuming the reservoirs on each side and the pathway of the hill are sufficiently big. Govaerts[7] has independently arrived at a similar mechanism in his analysis of the iso-osmotic diuresis of famine edema.

The exact timing made possible by precipitation of nephrotic diuresis by induced measles[31] has permitted Drs. Janeway, Hutchins, Wallace and myself to carry out detailed analyses of the dynamics at onset. Our findings corroborate older observations that a rise in plasma osmotic pressure occurs simultaneously with, but does not precede, diuresis of salt and water. The difficulty in obtaining complete urine collections from sick children has thus far blocked attempts to demonstrate large simultaneous decreases in albuminuria in all but one patient. In this patient, albumin

output decreased by a factor of 50 per cent two days before diuresis started. With better collection methods, we are now attempting repeated observations of this type which will be necessary in order to give any validity to a primary rôle for renal albumin permeability.

It is worth pointing out that the tendency of the nephrotic kidney to retain sodium (an old observation, recently re-emphasized by Luetscher[32] and sometimes considered a primary tubular defect in nephrosis) may also be a non-specific reaction of functionally normal tubules to profoundly low effective colloid osmotic pressure. Such sodium retention has been produced experimentally in dogs by plasmapheresis;[33] clinically, it is reversible both in profound nutritional edema and in idiopathic hypoproteinemia with normal capillary permeability by albumin therapy. The only edema which requires continuous salt restriction during albumin therapy is in a disease in which such therapy does *not* produce a sustained rise in effective osmotic pressure.

From the standpoint of therapy 1,500 Gm. (representing some 200 plasma donations) is highly uneconomical in order to obtain temporarily 15 to 30 Kg. of water from a patient, even if a process of recovery of albumin from the urine were worked out. The problem of intravenous protein therapy thus turns into a search for means to decrease urinary losses, either by changing renal permeability or by giving (or stimulating the body to produce) a protein of molecular size greater than albumin. Toward the first objective Dr. Emerson and I have administered large quantities of rutin to adults in various stages of nephrosis. A longer series will be required to evaluate this procedure. Toward the second goal massive administration of bigger plasma proteins has not yet been tried.

Rates of loss in the urine of various electrophoretic components, observed both by Luetscher[28] and in my own studies,[27] suggest that a molecular weight of 100,000 may be too small to be kept in the circulation. Indeed, the predominance of lipid-rich alpha and beta globulins in the sera of patients with nephrosis may well be due to the fact that gamma and other globulins of like weights (about 160,000) pass into the urine almost as easily as albumin. This is further emphasized by the fact that during spontaneous diuresis induced by measles in the nephrotic syndrome of children, serum albumin and gamma globulin levels all rise simultaneously and at rates roughly proportional to their normal concentrations. It is, of course, possible that there are simultaneous operating defects in synthesis of these components. This can best be determined after experimental settlement of the question of renal permeability shifts.

Clinical similarities between the nephrotic syndrome and the type of idiopathic hypoproteinemia based on increased capillary permeability raises the question as to whether or not these two syndromes are at opposite ends of a continuous spectrum. If this were the case, some degree of increased systemic capillary permeability might be expected in the nephrotic syndrome. The low edema fluid protein levels could be accounted by a small concentration gradient for albumin diffusion due to high urinary loss. To test this possibility in one classical severe nephrotic, Dr. Emerson and I, by huge dosages of albumin, have raised the blood level to approximately 3 Gm. per cent for a period of three days. Daily studies of edema fluid showed protein concentrations always below .7 per cent, a figure not at all comparable to the high levels of albumin in the edema of the idiopathic hypoproteinemia.

REACTIONS TO ALBUMIN

As currently processed and released, concentrated human albumin has a record of almost complete freedom from reactions. In my own experience patients who have experienced nausea, headache and malaise during treatment with certain globin and gelatin preparations have been absolutely asymptomatic on albumin. Occasionally, with doses over 50 Gm. a day mild headache is encountered. Administration in

quantity is obviously contraindicated in patients unable to tolerate consequent blood increases, notably in severe hypertension.

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Seminars on Hypertension

Physiology of Essential Hypertension*

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ELEVATION of the arterial blood pressure has been recognized in man for some fifty years as evidence of an abnormal state that may terminate fatally in congestive heart failure, apoplexy or renal insufficiency. In certain instances hypertension is caused by specific disorders of the kidney, the endocrine system or the brain, but in the majority of cases primary extravascular disease is not demonstrable.

For various reasons different terms have been applied to the latter group from time to time; these include hyperpiesia and essential hypertension, to indicate the importance of the higher intra-arterial pressure, and hypertensive vascular disease to avoid the implication that hypertension is more than one manifestation of an underlying disorder of the vascular system. Although each term is the result of a change in viewpoint, each bears in common the connotation that a single underlying disease entity is at fault. This concept finds support in a fairly uniform natural history and in distinctive anatomic changes. Moreover, a more or less consistent pattern of physiologic change has been identified with essential hypertension, setting it apart from other disorders associated with increased blood pressure. The following discussion is chiefly concerned with the physiology of the disease in man.

SYSTEMIC HEMODYNAMICS IN ESSENTIAL HYPERTENSION

The sphygmomanometer has played an extremely important rôle in making the diagnosis of hypertension a commonplace in medical practice. The information it yields is incomplete and often inaccurate since only systolic and diastolic pressures can be determined. Continuous accurate recording of intra-arterial pressure may be made by various instruments, such as the Hamilton manometer, the strain-gauge, the Lilly capitance manometer and the piezo-electric manometer. The tracings so obtained reveal a fluctuating pressure change, a series of pulses each of which presents certain characteristic repetitive phenomena. The systolic and diastolic pressures are but two points, the highest and the lowest pressures, in this cycle. For clinical purposes systolic pressure is defined as the pressure in the occluding arm cuff at which the Korotkow sounds over the brachial artery first become audible as pressure is released, or at which the pulse reappears in the radial artery. Simultaneous pressure determinations by sphygmomanometer and by an accurate membrane manometer indicate that systolic pressures yielded by the former may be 10 mm. Hg lower than the actual value.[1] This discrepancy may be laid to factors such as the area of compression by the cuff, the amount of tissue other than artery compressed and the physical properties of the vessel wall that influence the production of sounds or pulses. Diastolic pressure, on the other hand, taken as the cuff pressure at which the Korotkow sounds suddenly change in character (becoming muffled), is too high by as much as 20 mm. Hg.[1] Hence a somewhat more accurate figure is obtained at the level at which sounds fade away altogether.

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Both systolic and diastolic pressures are elevated in essential hypertension. Characteristic alterations in the pulse wave contour, which may be discerned indirectly in the pulse pressure, also occur. These changes are based upon dynamic alterations in the peripheral vascular bed and cardiac function.

In general, modern concepts of the hemodynamic factors concerned in the regulation of the arterial pressure agree in being based upon Hales' "air-chamber theory" and Poiseuille's laws of fluid flow in small tubes, in one form or another. According to Hales' hypothesis,[2] blood flows continuously through the vascular system, under a force derived entirely from the activity of the heart, by virtue of the elastic properties of the central arterial reservoir. This reservoir, probably embracing the entire arterial tree to the level of the arterioles, he likened to the air chamber (or Windkessel) of the old fashioned fire pump, in which air under compression maintained a head of pressure upon the water during the input phase of the pump cycle and forced a steady stream of water through the firehose. In the arteries, energy, stored during systolic distention of the arterial reservoir, is believed to return to the blood during diastole in the form of pressure and kinetic energy of flow as a result of the elastic recoil of the arterial walls. Although Hales' analogy is valid in a general sense, it must be applied with caution in a discussion of the physical characteristics of the central arteries, a complex contrasting sharply with the simplicity of the air chamber. Poiseuille's mathematic statement[3] of the relation between dimensions of the conduit, flow, pressure, viscosity and resistance in capillary tubes was based upon a study of the behavior of homogeneous, quasi-ideal fluids flowing through rigid tubes at velocities below the critical rates at which turbulency appears. Unfortunately these conditions do not obtain in the circulatory system and the determination of resistance to flow on the basis of Poiseuille's laws is at best approximative. Vascular resistance is usually expressed as the ratio between the pressure lost through the length of the system and the rate of blood flow through it. This simplified definition requires constancy of viscosity at all rates of blood flow and is vitiated by turbulent flow. It seems certain that the velocity of blood flow seldom exceeds the critical limit[4] but it is equally certain that blood viscosity may change markedly with minor changes in velocity.[5,6] Recent investigations[7] have shown that a linear relation between blood flow and arterial pressure never obtains even in the absence of humoral and nervous vasomotor activity. It has been found that the viscosity change at low velocities arising from the plastic and heterogeneous character of the blood is complemented at high rates of flow by a reduction in frictional resistance due to passive distention of arterioles and capillaries and to the opening of previously non-functioning collateral channels. The interpretation of peripheral vascular resistance in terms of the vascular cross section is approximately correct only when blood flow is constant. Since it has been observed[8] that the decrement in blood pressure is greatest in the arterioles, change in resistance calculated on the basis of flow and total pressure fall along the vascular bed may be referred to changes in arteriolar vasomotor activity, provided flow is constant.

In hypertensive disease the elevation in arterial pressure is usually ascribed to widespread arteriolar constriction because the total flow of blood through the body (cardiac output) remains within normal limits[9] and mean arterial pressure (or the average pressure throughout the cardiac cycle) rises. It is recognized that this inference is at best indirect although the facts upon which it is based are incontestable. Cardiac output may be accurately and directly measured today by the Fick method and there is no doubt of the validity of the observation that it remains at a normal level. The change in blood pressure is unquestioned. Other explanations for the increased pressure have been advanced but have proved unsatisfactory. It has been

suggested that more forcible contraction of the heart may impose a greater energy head upon the blood leaving the left ventricle. However, a more violent systolic contraction would be expected to contribute chiefly to kinetic energy and to do so over a shorter space of time unless there is a change in the volume of blood ejected or in resistance to output. In consequence the systolic phase of the cardiac cycle would be shortened, systolic pressure increased and mean pressure changed little if at all. Slight augmentation of the viscosity has been noted[10] but seems too small to account in any significant degree for the change in peripheral resistance. It is possible that undetected changes related to altered velocity may be important in the smaller vessels. Moreover, attention has recently been drawn to the importance of the character of the distribution of erythrocytes in the blood stream. "Sludging" or intravascular agglutination of red cells may cause marked changes in local capillary and arteriolar perfusion.[11] Such conglomeration of red cells has been observed in some patients with so-called "malignant hypertension" but there are no convincing data to suggest that this factor is important in the bulk of the patients with hypertensive disease. Pathologic changes in arterioles are often sparse and scattered. Studies of arterioles from muscle and various organs indicate that hypertensive disease is associated with a somewhat more severe grade of medial hypertrophy with or without collagenous degeneration and intimal hyperplasia than one finds in normal individuals of the same age group.[12–15] This arteriolar lesion occurs frequently in sites that are rarely affected in the normal, such as the kidneys, liver and gastrointestinal tract but it cannot be shown that these changes *per se* impose increased resistance to blood flow. Indeed in some cases it is possible that the lumina are actually increased in diameter. Hence it is necessary to posit active arteriolar vasomotor activity such as one may occasionally observe directly in retinal vessels.

It is generally agreed that the vascular lesions are a manifestation of aging rather than an effect of increased intravascular tension. The fact that pulmonary arteriolosclerosis tends to develop only in the presence of pulmonary hypertension has been cited in support of a direct effect of elevated pressure upon the blood vessels,[16] but pulmonary hypertension is not entirely analogous since it is usually associated with stasis and cardiovascular or pulmonary inflammatory disease. Moreover, lesions of the small arteries and arterioles in the systemic system may occur without hypertension; conversely, hypertension of long duration may be associated with little vascular damage. Hence, the two conditions are probably independent. Since arteriolosclerosis is usually more severe among hypertensives, it is believed that hypertension may accelerate aging but the conclusion that senescence may predispose to the development of hypertension seems equally valid. Certainly the incidence of the disease increases with age, affecting approximately 40 per cent of the population over the age of fifty.[17] Arteriosclerosis is also more common in these patients than it is in normotensives of the same age. The central arteries become tortuous, dilated and inelastic. Arteriosclerotic disease of the cerebral and coronary arteries ultimately causes death in a large percentage of patients.

The mean arterial pressure is not affected by the changes in the large arteries[18,19] chiefly because there is an expansion rather than a contraction in the total arterial cross section. Moreover, the arteries probably impose little resistance normally to the flow of blood from the heart to the arterioles.[20] Although changes in arterial elasticity do not alter the mean pressure, they do affect the pulse wave contour. It is obvious from what has been said that increased rigidity with decreased distensibility of the arteries would interfere with energy storage during systole. As a result the systolic pressure would increase, other factors remaining constant and the pressure curve would drop sharply during diastole. In such a

case, as in advanced arteriosclerosis of the aorta, the mean pressure would not rise while the diastolic pressure would remain unchanged or fall slightly. Theoretically there is excellent reason to believe that as long as the stroke volume and pulse rate (or cardiac output) remain constant, an increase in the pulse pressure always denotes an augmentation in the arterial elasticity coefficient. In hypertensive disease the pulse pressure is nearly always greatly increased even in the absence of arteriosclerosis. There is considerable disagreement regarding its significance. Studies of pulse wave velocity in the great vessels, on the basis of the classic mathematic formulations made by Moens and later by Bramwell and Hill, of the relationship between the velocity of the pulse transmission along vessel walls and the elastic properties of the vessels indicate a decreased distensibility of arteries in the presence of hypertension. Wiggers and Wégria[21] attribute this to an active change, probably as a result of muscular contraction in the vessel walls, since they found that the aortic capacity may decrease in dogs during arterial hypertension. Other workers[22,23] have shown that increased vascular resistance with an elevation of mean diastolic pressure leads to a continuous distention of the arteries that must *per se* reduce further distensibility, perhaps sufficiently to account for the increased pulse pressure of hypertension. This question remains unsettled, particularly since an accurate method of measuring arterial elasticity is lacking. The measurement of pulse wave velocity is often quite difficult technically. Questionable assumptions regarding the length of the vessels and the timing of impulses are required. The analysis of the pulse wave contour is also fraught with uncertainty since many other factors, such as reflected waves, regurgitant flow and altered systolic ejection velocity, may contribute to the observed changes.

The idea that an active vasomotor element may contribute to the observed decrement in arterial elasticity is in harmony with the view that increased motor activity throughout the entire vasculature is characteristic of hypertensive disease. Since the systemic circulation time remains normal,[24] it is probable that there is a normal blood flow everywhere in the body, despite the marked elevation of perfusing pressure, without hyperemia in any significant portion of the vascular bed. Moreover, the blood flow through every major circuit has been measured in patients with essential hypertension without disclosing evidence of selectivity. Certain experiments[25] suggest that the musculature of the veins may also partake in the generalized increase in tonus with resultant disturbance of their function as blood reservoirs.

It is frequently asserted that hypertensives are "hyper-reactors" responding to sundry stimuli by excessive elevations of blood pressure and by disproportionate emotional patterns. Clinical experience supports this claim but it has proved difficult to place the phenomenon upon a quantitative footing. Various tests have been devised to elicit hyper-reaction in a standard manner. The pressor responses to immersion of one hand in ice water (4°C.),[26] to excitement,[27] to the Flack maneuver (prolonged exhalation against 20 mm. Hg pressure)[28] and to physical work[29] have been widely studied with divergent and conflicting results.[9,30] In addition it appears that hypertensives may display more striking reductions in blood pressure than normotensives during the pyrogenic reaction[25] or following the administration of depressor drugs such as the nitrites[31,32] and mecholyl.[33] These excessive pressor and depressor responses are usually discussed in terms of vasomotor activity but insufficient data are at hand to permit an accurate appraisal of the hemodynamic adjustments. Obscure changes in cardiac output and in the relation between output and peripheral resistance may be as important in many instances as the intrinsic changes in vasomotion. The behavior of different parts of the vascular bed during these reactions also needs further study. There is little doubt that widespread vasoconstriction or vasodilation

can occur and that the peripheral resistance is not fixed in essential hypertension.

The hemodynamic factors involved in the production of other varieties of hypertension require investigation. Vasoconstriction is probably an important cause of elevated pressure in hypertensive disease of pregnancy, coarctation of the aorta,[34] Cushing's syndrome, glomerulonephritis and other forms of renal disease, but careful quantitative studies are too few to permit accurate appraisal. These conditions are to be differentiated from essential hypertension on the basis of manifestations other than the level of the arterial pressure, the character of the pressure pulse contour or the pattern of vascular reactions to stress. The excess epinephrine production of pheochromocytoma may result in a persistently elevated blood pressure closely resembling essential hypertension. However, here characteristic vascular reactions are demonstrable since histamine may elicit a striking augmentation of arterial pressure[35] and benzodioxane may have a depressor action.[36]

Many important advances in the study of human hypertensive disease during the last twenty years have come from studies of individual organ circuits. These studies are important not only because they provide evidence upon which to base conceptual thinking but also because they shed light upon the manner in which arterial hypertension gives rise to tissue damage that may ultimately prove fatal. From the standpoint of prognosis the most important organs affected are the heart, the brain and the kidneys, in the order named. The splanchnic and muscular vasculatures are also important because they may accommodate so large a proportion of the total blood flow, but pathologic conditions in these areas seldom, if ever, develop as a result of hypertension

THE HEART IN ESSENTIAL HYPERTENSION

Sooner or later, nearly every hypertensive patient presents evidence of cardiac abnormality. The heart increases in size as a result of dilation and hypertrophy of the left ventricle although the right ventricle may participate in the process. Congestive heart failure may make its appearance insidiously with slowly developing exertional dyspnea, orthopnea and peripheral edema or abruptly with paroxysmal dyspnea and pulmonary edema. Cardiac hypertrophy and decompensation are usually ascribed to increased work; since the cardiac output remains normal in the presence of the elevated mean arterial pressure, heart work apparently increases in proportion to the change in blood pressure. Moreover, work may be enhanced to some extent by an augmented kinetic energy of systolic outflow as a result of more rapid ejection.[37] The kinetic energy factor cannot be estimated quantitatively in man but it appears to be of relatively little importance. Effective heart work cannot be calculated on the basis of the product of mean arterial pressure and cardiac output chiefly because it is impossible to measure the mean pressure in terms of periods longer than a few hours. The heart is continuously exposed to the effect of elevated pressure and heart work must be estimated on the basis of the load imposed over a long time in order to evaluate the part it plays in causing cardiac hypertrophy. Single isolated measurements of the blood pressure are useless for this purpose. There is considerable variation in the pressure level from time to time. Perera[38] has found that the blood pressure tends to fall and become stabilized at a lower level some time after repeated measurements are begun by the same person. It immediately departs from this level when a stranger takes the pressure or when minor emotional stimulation occurs. Ayman and Goldshine[39] found a similar difference between blood pressures taken at home by the properly instructed patient and those taken in the clinic by a physician. The cardiac output is also very variable and even more difficult to follow over any length of time. Finally, current methods of estimating cardiac work fail to make due allowance for the fact that work is performed only during systolic ejection against the changing

pressure head prevailing at the aortic valve, and it appears that a revision of method will be necessary to obtain more accurate values.[40] Thus it is obviously impossible at present to determine accurately the load under which the heart labors but, nevertheless, it seems likely that myocardial hypertrophy is best explained on the basis of increased work and energy production. Whether cardiac decompensation is the result of a failure of energy production or of a defect in energy utilization remains a debated and unsettled problem.

Another factor that cannot be neglected in considering the pathogenesis of cardiac hypertrophy and decompensation during essential hypertension is the state of the coronary circulation. Disease of the coronary vasculature alone may be sufficient to cause marked hypertrophy and even congestive heart failure. There is little doubt that coronary insufficiency occurs more frequently among hypertensives than among a non-hypertensive population of the same age group.[9,13] It is generally conceded that this is a result of the acceleration of the aging process by hypertension rather than a direct effect of elevated arterial pressure. Arteriolosclerosis is relatively uncommon[12–14] but arteriosclerosis occurs frequently and leads to myocardial infarction in about 14 per cent of patients with essential hypertension. It seems not unlikely that the coronary arterioles participate in the generalized vasoconstriction characteristic of the disease, but as yet measurements of the coronary flow in man have not been made and the question remains unanswered. There is some evidence that interference with blood flow may account for certain electrocardiographic abnormalities.

Electrocardiographic changes occur in most patients. The so-called "pattern of left ventricular strain," consisting characteristically of inversion of the T wave in the first and possibly the second limb leads usually associated with S-T segment depression and left axis deviation, has been considered by some as typical of the disease.[41,42] Recent studies[43,44] have shown that these manifestations are not related to the severity, duration or character of the blood pressure, to cardiac hypertrophy or to prognosis when the changes due to myocardial infarction and digitalis are eliminated. Most workers[41,42] consider the strain pattern a result of the pressure stress upon the heart, a view supported by the dramatic return of the ECG to normal following return of the arterial pressure to normotensive levels after lumbodorsal sympathectomy.[45] However, Filley[44] has found a fairly good correlation with the presence of arteriosclerosis of the coronary arteries and he suggests that "the relative sufficiency of these vessels is increased by reducing the work of the heart concomitant with the lowering of arterial pressure." He failed to find any prognostic significance in the strain pattern, however, and the significance of the reversal after sympathectomy is unknown because postoperative follow-up has not yet been sufficiently long in most cases. There is evidence that the vascular disease may persist and progress even after the reduction in blood pressure.[46]

Only the left ventricle appears to be subjected to stress during essential hypertension. On direct measurement[47] the right ventricular pressure in five hypertensives was found to fall within normal limits, indicating the absence of increased arteriolar resistance in the pulmonary bed. The altered ballistocardiographic complex of hypertensive disease probably results from the exaggerated pressure difference between the two ventricles (one expelling blood into a system in which the pressure is elevated and the other into a normotensive system) that leads to asynchrony of ejection and, in consequence, a splintering of the ejection wave ("early M" shaped type).[48] The venous pressure is normal throughout the course of the disease unless congestive failure supervenes. Hence it may be posited that right ventricular filling is not disturbed and that venous hemodynamics are unaltered. However, the notable tendency of hypertensives to respond to spinal anesthesia,[49] the pyrogenic reaction[25] and in-

creased intra-abdominal pressure[50] with striking reductions in blood pressure may be based in part upon a defect in the mechanisms that provide for adequate return of blood to the heart.[51,52]

NERVOUS SYSTEM IN ESSENTIAL HYPERTENSION

Vascular disorders of the central nervous system occur quite frequently in essential hypertension. The catastrophes of massive hemorrhage or thrombosis account for some 15 per cent of deaths due to the disease.[9] Other less severe manifestations of cerebrovascular disturbances may totally disable many patients. Transient episodes of sensory and motor disturbances, aphasia or amaurosis, are seen especially in the accelerated phase, or malignant nephrosclerosis. Headaches are particularly common and disagreeable. These neurologic derangements are by no means peculiar to essential hypertension for they complicate the course of hypertension due to any cause and occur in the absence of hypertension. Thus the following remarks concerning the pathologic cerebrovascular physiology of essential hypertension are probably applicable to other hypertensive states, but since so little is known regarding systemic hemodynamics in these conditions, it is impossible to do more than indicate here the obvious clinical similarities.

The cerebral vasculature suffers the same changes that occur elsewhere in the vascular system. Arteriosclerosis of the large vessels is common although there is no connection between the severity and duration of the elevated blood pressure and the arterial changes.[53] Here in contrast to the heart the disease leaves its mark in the arterioles. Intimal hyperplasia, medial hypertrophy and degeneration and occasionally adventitial proliferation are found in varying degree.[12,14,15,53,54,55] Evidence of active vasoconstriction, somewhat in excess of that in other parts, has been brought forward by Kety and Schmidt.[56] Using an ingenious method[57] based on the cerebral uptake of nitrous oxide from the blood, these workers found that cerebral blood flow and cerebral oxygen consumption were slightly below average normal in all of a series of five hypertensives (mean arterial pressure 143 mm. Hg). Thus in the face of greatly augmented blood pressure, the cerebrovascular resistance doubled, probably because of vasomotor activity, since it seems unlikely that so large an increment in resistance would develop on the basis of the demonstrable arteriolar disease. However, this point must be investigated and evidence of reversibility sought.

The massive cerebrovascular lesions of hemorrhage and thrombosis chiefly involve the larger arteries. Scheinker[58] has recently called attention to the possibility that venous disturbances may be important. Focal or diffuse lesions of the brain, resulting either from capillary hemorrhage or arteriolar occlusion, frequently give rise to clinical manifestations. One syndrome, characterized by headaches, dysesthesia, fleeting palsies, personality changes, intellectual impairment and a prolonged progressive course, has been described as "chronic hypertensive encephalopathy" by Davison and Brill.[59] Marked arteriolar disease, leading to widespread areas of demyelinization, focal hemorrhages and moderate gliosis, is always found. A more acutely developing clinical complex, of severe headache, convulsions, coma, transient defects of motor activity and sense perception, and a marked elevation in blood pressure ("hypertensive crisis") has been described by Oppenheimer and Fishberg[60] who claim that it may develop in the absence of cerebral lesions and that arteriolar spasm alone may be at fault. The evidence for this hypothesis is indirect and inconclusive. The absence of demonstrable disease is rare indeed[61] but it is possible, of course, that vasospasm may be important even when structural changes have occurred. Cerebral edema may develop rapidly and give rise to headache, convulsions and coma without manifestations of focal involvement at any time as part of the picture of acute or chronic encephalopathy. Opinions are varied and contradictory regarding its place in the

pathogenesis of these syndromes.[62] Studies of cerebral blood flow during encephalopathic seizures are awaited with great interest.

The typical retinal involvement of hypertensive disease may be considered as one manifestation of these encephalopathies since the eye is closely allied in origin to the brain and its investitures. Arteriolosclerosis, characterized chiefly by intimal proliferation and lipoid or hyaline deposits, affect the retinal and choroidal arterioles although in the former intimal proliferation is believed to be uncommon.[63] A reduction in the caliber of retinal vessels results not only from these lesions but also from vasoconstriction that may develop in localized areas under direct observation.[64,65] Sclerosis of the common arteriovenous wall at crossovers may result in partial or complete venous obstruction.[66] Hemorrhages and areas of degeneration may appear as a result of the vascular lesions.[66] Edema of the retina and nerve head may occur in association with elevated spinal fluid pressure, but the local vascular disturbances alone may be sufficient to cause edema.[53,67,68] Diffuse retinal disturbance, occlusion of retinal arteries or veins, and intracerebral involvement of visual centers and pathways may seriously affect sight.

Headache is a common concomitant of these disorders and is one of the most frequent complaints of hypertensive patients even in the absence of demonstrable cerebrovascular involvement. It is occasionally so severe as to prove completely incapacitating, but in most patients it is relatively mild, responding readily to small doses of the common analgesics. The pain is frequently unilateral and migrainous in character. Indeed, it appears to be etiologically related to migraine insofar as both types seem to be caused by dilation and distention of cerebral arteries, particularly the branches of the external carotid. Wolff[69] claims that pain of this type results from decreased tone of the arteries that leads to greater stretching of the arterial parieties with resultant activation of pain fibers. Many patients give a history of headache long antedating the appearance of hypertension. It is to be expected that the higher intra-arterial pressure level would result in augmented stretching of the vessels and intensified headache in such persons, whereas in others diminution of tone compatible with comfort at a normal pressure level might prove a cause for pain at a higher intra-arterial pressure. Ligation of branches of the external carotid has been shown to alleviate hypertensive headaches in certain cases.

Personality disorders are commonly associated with encephalopathies but certain changes may occur independently of cerebral disorders. Intensive investigation of the personality pattern in a few individuals suggests that hypertensives tend to display "exaggerated dependent strivings, submissiveness coupled with stubborness, feelings of weakness and defenselessness, suppression of hostility, fear of injury, and emotional detachment" that may lead to "acute emotional disorders . . . resulting from the inefficiency of the patterns of defense against anxiety and the weakness of repressive mechanisms."[70] It has been claimed that essential hypertension may be a somatic "manifestation of a psychoneurotic condition based on excessive and inhibited hostile impulses."[71] Unfortunately, studies of large numbers of "normal" persons for purposes of control and of the same individual before and after the onset of hypertension have not been made and do not at present appear practicable. Patients frequently assert that they are more "nervous" and tense following the appearance of hypertension, even when they have not been informed of the presence of the elevated blood pressure. Rest, relaxation and freedom from care have long been known to have a beneficial effect in lowering the arterial pressure. Moreover, elimination of supratentorial activity by general anesthesia or deep narcosis frequently has a striking depressor effect.[72] The emotional component is so variable from person to person and from time to time that it can scarcely be accorded more than an incidental rôle in the patho-

genesis of essential hypertension. On the other hand, abnormal subcortical activity involving the medullary vasomotor centers or the autonomic nervous system may be very important and may be subject in a measure to influence by higher centers.

Cerebral anemia, increased intracranial pressure and experimental denervation of the carotid sinus will give rise to a sustained arterial hypertension that is apparently mediated through the autonomic nervous system. But there is no evidence that the first two figure prominently in essential hypertension. The physiologic pattern of the last has no proved counterpart in man. Neurogenic hypertension in animals is characterized by a marked increase in cardiac output, tachycardia, augmented blood flow in the extremities and marked lability of blood pressure resulting from fluctuations in cardiac output.[73,74] Nonetheless, the development of excessive sweating, flushing and whealing, and vasomotor instability in some patients, indicates that autonomic activity may be increased. Dock, Shidler and Moy[75] have found that decerebration of hypertensive animals results in a return of pressure to normal, despite continued reactivity of the vessels to pressor drugs. They suggest that the medullary vasomotor centers essential in the regulation of arterial pressure may be "set" at higher levels, perhaps initially by the action of some humoral agent. A somewhat similar notion has been put forward by Ogden and his co-workers[76] who believe that the arterial pressure once elevated is sustained by the action of the sympathetic nervous system. Thus, reduction in blood pressure following high spinal anesthesia,[76] autonomic blockade[77] and lumbodorsal sympathectomy[78] has been considered by some to reflect a specific correction of the hypertensive state through removal of excessive neurogenic vascular stimulation. This conclusion is disputed because the blood pressure is unaffected in a significant proportion of patients, the depressor effect may be transient and vasomotor tone is not specifically reduced in the vasculature of the extremities and kidneys. But that there is a reduction of total peripheral vasoconstriction and a fall of blood pressure to normal in most patients is undeniable. Hence, it appears that if not granted a primary rôle in the pathogenesis of hypertension, the autonomic nervous system must at least be accounted a major factor in dictating the pressure level.

THE KIDNEY IN ESSENTIAL HYPERTENSION

For many years the kidney has occupied a central position in any discussion of essential hypertension, both because renal disease is so often associated with an elevated blood pressure and because hypertensive disease may terminate in marked renal damage. Moreover, the renal circulation is an extremely important component of the systemic vascular bed. Some 1,200 cc. of blood, or approximately one-quarter of the cardiac output, flow through it each minute.[79] Because of this large circulation the kidney plays a major rôle as a circulatory buffer. Its vasculature is highly reactive, responding to emotion,[79] pain,[80] exercise,[81] blood loss[82] and the upright position[79] by vasoconstriction that operates to support the arterial pressure and to provide blood for the perfusion of more needy circuits. Whether defective activity of this kind is concerned in the pathogenesis of essential hypertension or whether it predisposes the renal vascular bed to damage by hypertension is unknown.

Goldblatt[83] has brilliantly demonstrated that constriction of the renal arteries causes arterial hypertension in animals either by the production of renal ischemia or by interference with intrarenal hemodynamic adjustments. It appears that a similar mechanism may be concerned in the pathogenesis of some, but not many, instances of human hypertension.[84] In the remainder, arteriolar constriction and, ultimately, ischemia of renal tissue are clearly demonstrable, but it is impossible to say whether arterial hypertension precedes or follows the vasomotor change.

The clearance methods devised by Homer Smith and his co-workers[85] for the safe and atraumatic measurement of renal blood flow in human subjects have provided a wealth of information regarding the behavior of renal circulation in the course of essential hypertension. These procedures are based upon the belief that the renal clearance of diodrast or sodium p-aminohippurate (PAH) is a measure of renal blood flow, and require the assumption that all, or almost all, of the measuring substance is cleared from the blood perfusing the kidney. This assumption has proved valid in most hypertensive patients. Analysis of renal venous blood, obtained by venous catheterization during the determination of PAH clearance, indicates 85.4 to 100 per cent extraction of PAH even when renal damage is relatively severe.[86] Since PAH and diodrast clearances are identical, diodrast must be extracted to the same extent. Hence, data based on the clearance technics may be used as a basis for discussion of renal circulation in essential hypertension.

In almost one-half of sixty hypertensives studied by Goldring and his co-workers[87] the renal blood flow was found within normal limits. Only three of these figures exceeded the normal mean value and it was concluded that the renal blood flow tends to be reduced. Intravenous administration of pyrogenic agents evoked a marked increase in blood flow, equal to that observed in normal persons in eighteen of twenty of their subjects. Consequently, a reversible vasoconstriction rather than a fixed vascular obstruction must be called upon to account for the failure of renal blood flow to increase in proportion to the elevation of the arterial pressure under which the kidneys are perfused. Both kidneys are equally affected of the majority of cases.[88] Unilateral renal or ureteropelvic disease appears to be an uncommon cause of hypertension and unimportant as an etiologic factor in essential hypertension.[84]

Considering the fact that renal blood flow tends to fall within normal limits, ischemia of renal tissue is probably not marked in most cases. However, ischemia of a part of the kidney may be masked by hyperemia of the remainder. Blood flow must be examined, therefore, in relation to the mass of kidney tissue it perfuses.

The renal tubular tissue can be estimated quantitatively in terms of its maximal reabsorptive and excretory capacities. Diodrast and PAH are excreted with great efficiency when they are present in low concentrations, but at higher concentrations the excretory rate reaches a maximum which appears to be dependent upon the mass of functioning tubular tissue. The maximal rate of transfer from blood into the tubular urine is referred to as the transfer maximum or Tm of the substance in question. Glucose is reabsorbed by a similarly limited transfer mechanism and may be employed to estimate the quantity of tubular tissue processing glomerular filtrate.[89] Many substances, e.g., most electrolytes, do not lend themselves to this usage because they are handled by the tubular cells in a different manner and are not removed from blood or filtrate at a constant fixed rate, independently of the blood level, above certain relatively high concentrations.

The relation between diodrast clearance and diodrast Tm (blood flow-Tm ratio) has been used to assess the distribution of blood to the renal parenchyma. In most hypertensives this ratio is somewhat depressed below the normal mean figure, but in general it does not deviate greatly from the normal range.[87] It may be inferred that there is a tendency for relative ischemia to develop. Since diodrast Tm may be normal in many patients with well established hypertensive disease, the ischemic process appears to involve the kidney as a whole without shunting of blood away from a significant mass of parenchymal tissue through by-passes similar to those observed by Trueta and his co-workers.[90] Even when extensive damage has occurred and diodrast Tm is greatly reduced, the degree of relative ischemia does not appear to be marked. However, there is a suggestion that ischemia may bring about parenchymal destruction

in the observation that diodrast Tm increased more than 10 per cent in seven of twenty hypertensives during the pyrogenic reaction.[87] This phenomenon may be attributed to more adequate perfusion, during hyperemia, of tubular tissue formerly receiving little blood. Such regions of focal ischemia are also detectable by other means[89] and it may be surmised that atrophy of tubules with ultimate replacement by fibrous tissue occurs in these sites. Since the extraction of PAH continues to be normal or nearly so, even when extensive parenchymal destruction has resulted in manifest renal insufficiency, blood apparently perfuses normally extracting tubular tissue almost exclusively. Thus cellular dysfunction probably follows upon the withdrawal of the blood supply as a result of vascular constriction and occlusion. In view of the high PAH extraction true arteriovenous shunting must be excluded as a possible cause of localized ischemia. Rather it appears that focal ischemia, possibly resulting from the development of structural lesions, is engrafted upon a state of diffuse ischemia due to vasoconstriction. Although diffuse and focal ischemia are probably of primary importance in producing renal structural damage, they are not necessarily or consistently present in essential hypertension and appear to be consequences rather than causes of the disorder.

The renal functional alterations of essential hypertension correlate well with the pathologic pattern. In about 85 per cent there is no evidence of parenchymal damage and few or moderate changes in the vasculature.[14] In the remainder there is a varying degree of tubular atrophy, associated with occasional hypertrophy, of the proximal segment and fibrosis, which may be sufficiently extensive in occasional instances to produce contraction of the kidney and fine granularity of its surface. The vascular lesions are frequently striking. The small arteries and arterioles show a degree of arteriolosclerosis rarely encountered in the normal although from 3 to 17.5 per cent of various series[12,14,91] fail to present any vascular lesions whatever. The vascular damage is usually not so diffuse that it can be accounted a significant cause of increased resistance to flow. It is characterized by proliferation of the intima, the appearance of subintimal hyaline and lipoidal deposits and hypertrophy of the media. These changes may produce no narrowing of the lumen and may even be associated with dilatation, especially of the afferent arteriole. Glomerular involvement is not striking and obliteration appears to follow destruction of the tubule. Thus atrophic tubules are frequently attached to glomeruli of normal size.[93]

Glomerular filtration rate tends to remain within normal limits even when renal blood flow is greatly reduced. In part, this maintenance of filtration may be ascribed to the presence of "impotent" tubules that fail to have any excretory activity and serve merely as conduits through which filtrate passes. Such an interpretation is in harmony with the anatomic changes described above. However, the normality of filtration, when blood flow is reduced by vasoconstriction without parenchymal destruction, must involve a local hemodynamic adjustment which operates to increase the filtration pressure so that a normal volume of filtrate is expressed from the smaller minute-volume of plasma. Since arterial pressure is elevated, it may be assumed that the afferent arterioles do not constrict sufficiently to prevent the transmission of the elevated head of pressure to the glomerulus. Hence, the chief locus of vascular resistance must lie in the post-glomerular vascular bed, probably in the efferent arteriole. Lamport[94] argues, on the basis of mathematic considerations, that afferent arteriolar vasoconstriction is a more important factor. It is possible that this claim is tenable in certain cases in which normal values for filtration and blood flow have been observed, but in the vast majority of patients with essential hypertension efferent arteriolar vasoconstriction must be assigned a major rôle. It has already been noted that intrarenal vasoconstriction may

be eliminated during the pyrogenic reaction.[87] However, other means of interfering with vasomotor activity have been less successful.

Interruption of autonomic activity by tetraethylammonium bromide,[77] high spinal anesthesia[49] and lumbodorsal sympathectomy[9] does not influence the renal blood flow. The fact that the blood flow remains unchanged even when blood pressure is lowered by these means indicates that vasodilation is induced in proportion to the level of arterial pressure, but this phenomenon may be attributed to local autonomous adjustment of the renal circulation rather than to the elimination of vasoconstrictor impulses. Indeed, if the blood pressure is greatly reduced, the renal blood flow may fall markedly. These facts indicate that the renal vasoconstriction of essential hypertension is mediated through a humoral mechanism or local reflex neuromuscular action rather than through nerve pathways. In this connection it is of interest that various pressor agents, including epinephrine,[95] ephedrine,[95] paredrinol,[95] angiotonin[96] and S-methylisothiourea[97] evoke a similar renal hemodynamic adjustment.

Certain discrete activities of the renal tubules seem to be specifically affected. Goldring and his co-workers[87] noted that maximal diodrast excretion was reduced earlier in the disease than maximal glucose reabsorption and they suggested that the underlying intracellular dysfunction might be concerned in some way with the pathogenesis of hypertension. Sodium and chloride reabsorption are also disturbed. As a group hypertensive individuals withstand acute salt deprivation with aplomb in striking contrast to normal individuals.[98] Perhaps a more efficient sodium reabsorption mechanism accounts for this difference by preventing salt loss during deprivation. However, Farnsworth[99] has presented evidence that the hypertensive kidney reabsorbs chloride less efficiently than the normal. The discrepancy may arise as a result of either a dissociation between sodium and chloride reabsorption or more advanced renal damage in Farnsworth's cases, in most of whom glomerular filtration was significantly reduced. The higher urine flows relative to filtration rate among her patients may have been important also in enhancing chloride clearances. In any case an alteration in tubular disposal of sodium and chloride appears to develop in hypertensive disease. This fact, among others, has directed attention to the adrenal cortex.

It is now well known that the adrenal cortex is intimately concerned with the regulation of tubular reabsorption of sodium and potassium. Adrenal cortical insufficiency leads to excessive salt loss with attendant reduction of plasma volume and ultimately fatal shock. Salt replacement and desoxycorticosterone acetate administration brings this situation under control. But continued treatment over a period of years results in the development of hypertension in a high percentage of cases.[100] It has been shown that desoxycorticosterone acetate is the chief offender since control with salt alone is followed by a return of blood pressure to normal. Hypertensive patients, without adrenal cortical insufficiency, respond to administration of desoxycorticosterone acetate by further elevation of blood pressure.[101] This reaction occurs in normal persons but it is delayed and less impressive. An adequate salt intake appears to be necessary, since salt depletion prevents the rise in pressure.[38] It is noteworthy that rigid restriction of salt intake appears to exert a slight depressor effect in hypertensives.[102] These facts suggest that the adrenal cortex may play a part in the pathogenesis of essential hypertension. A search for adrenal cortical lesions has been made but the results have been conflicting and disappointing.

The various disturbances of renal function described above are not easily detected by the means at the command of the clinician. Proteinuria is rather common and increases in severity as the disease progresses. In a small number of cases renal insufficiency may develop and cause death, but in the majority, renal function, as judged by

urinary concentrating power, phenolsulphonphthalein excretion and urea clearance, is not greatly disturbed through the course of the disease.[9] In most instances of renal insufficiency and uremia the renal parenchymal damage is a result of the development of malignant nephrosclerosis.

This disorder may suddenly appear in previously healthy individuals or in the course of the usual slowly evolving hypertensive process.[13] The blood pressure rises to a very high level. Congestive heart failure, uremia or a cerebrovascular accident may cut short the course in a matter of months after onset. Uremia always appears apparently as a result of a diffuse necrotizing arteriolitis that chiefly affects the renal arterioles. Here, too, there appears to be intense and widespread renal vasoconstriction which is evident in the marked reduction in renal blood flow. The extraction of PAH has been depressed in three cases of this type studied in this clinic, possibly indicating the operation of arteriovenous shunts or the presence of severely damaged tubular tissue remaining under perfusion. Whether this fatal disorder is simply an intensification of the vascular disease underlying essential hypertension or whether it is an entirely different process remains disputed. A similar acceleration of the evolution of vascular lesions and of renal damage may appear in the course of hypertension caused by glomerulonephritis[103] or pyelonephritis.[104]

The renal functional derangement of essential hypertension appears to be based chiefly upon a disturbance in the renal circulation. Active vasoconstriction, that is at least partially reversible, not affected by renal denervation and localized preponderantly in the efferent arteriole, is apparently the basis for structural alterations. Reduction in renal plasma flow without a change in glomerular filtration rate is a distinctive feature and often serves to differentiate the disorder from other entities causing hypertension in which filtration may be greatly reduced, such as chronic diffuse glomerulonephritis[105] and chronic pyelonephritis.[106] A similar functional pattern has been observed in the presence of hypertension caused by coarctation of the aorta.[107]

ABDOMINAL VISCERA IN ESSENTIAL HYPERTENSION

The abdominal viscera are not disturbed by the processes of essential hypertension. Gastrointestinal disorders are relatively uncommon. Liver function is normal throughout the course of the disease although jaundice and other manifestations of hepatic dysfunction may occur independently or as a result of congestive heart failure. This apparent immunity of the splanchnic circuit is more astonishing when one considers its place in the total circulation. Measurements of hepatic venous outflow (or total splanchnic blood flow) by a method based on the measurement of hepatic bromsulfalein clearance indicates that one to two liters of blood, a large fraction of the cardiac output, leave the splanchnic bed each minute in normal persons.[108] Estimation of hepatic blood flow in patients with essential hypertension has shown no significant deviation from normal.[109,110] This can mean only that vasoconstriction is present, probably affecting the hepatic and mesenteric arterioles. Since there is no evidence of an abnormality in portal venous pressure, it may be presumed that the process does not extend into the post-arteriolar vessels. Wilkins and his coworkers[110] claim that splanchnic vasoconstriction is released by lumbodorsal sympathectomy because hepatic blood flow may increase markedly when resting blood pressure is not lowered. Hepatic flow changes little or not at all when blood pressure is lowered by the operation. Thus it appears that the splanchnic circuit participates in the generalized vasoconstriction, without incurring the damaging lesions that appear in the brain and kidney, although arteriolosclerosis may be widespread in the liver and pancreas.

MUSCLES AND SKIN IN ESSENTIAL HYPERTENSION

Disorders of the muscles and skin occur no more frequently among hypertensives

than among the population at large. A florid, ruddy complexion has often been considered a distinguishing characteristic although it apparently has little significance, if indeed it is at all connected with the disease. Some hypertensives complain of cold, clammy extremities, but quantitative studies of the water loss from the surface of the finger tips have shown no difference between hypertensives and normal subjects.[111] The skin temperature also falls within normal limits.[112] Thus, there is no evidence of altered circulation or abnormal sympathetic activity in the skin.

The blood flow through the extremities, which may be considered for practical purposes made up solely of skin and muscle, is normal in hypertensives, according to most studies,[113–116] indicating an increased resistance to flow approximately proportional to the increment in arterial pressure. Since blood flow increases during warming to the same extent as in the normal, the increased resistance is considered to be vasoconstrictive rather than structural in origin, and apparently is not mediated by the autonomic system since sympathetic vasodilatation under these circumstances would be expected to cause excessive flow. A more effective method of inducing vasodilatation has been employed by Wilkins and Eichna.[116] Vascular occlusion for a period of five minutes elicits what appears to be a constant maximal dilatation, and blood flow increases markedly (reactive hyperemia) in proportion to the existing level of blood pressure. Thus elevated arterial pressure due to hypertensive disease causes an enhanced blood flow during reactive hyperemia corresponding to that observed in normal persons in whom blood pressure has been increased to the same level with paredrinol. Sympathectomy of the limb does not alter this response. The fall of pressure following lumbodorsal sympathectomy is attended by a proportionate decrease in hyperemia flow. Wilkins and Eichna found that hyperemia flow returned to the preoperative level several months postoperatively in some patients, despite continued normal blood pressure. This phenomenon may indicate slow relaxation or dilatation of constricted arterioles after return of the blood pressure to normal. Since the method of measurement is so unreliable, the range of normal variation so wide and the appearance of spontaneous variations in flow so common, these workers regarded the evidence as insufficient to prove that excessive vasoconstriction occurs in the peripheral vascular bed.

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From a physiologic standpoint, essential hypertension is a vascular disease characterized by generalized arteriolar vasoconstriction which results in a sustained elevation in arterial pressure. It is possible that smooth muscle in the arteries and veins also undergoes contraction but evidence of this is scanty and inconclusive. In many cases the arterioles of the kidney and possibly the brain are involved to a greater extent than arterioles elsewhere in the body. Possibly because of such excessive constriction the vasculature and tissues of these organs suffer pathologic changes that are equalled or exceeded only in the heart. Cardiac damage is probably related to the burden of maintaining a normal flow of blood through the body against an augmented peripheral resistance.

Both the kidney and the nervous system have been implicated as possible primary sites of involvement. The chronologic relationship of vascular disturbances in these organs to the onset of hypertension has not been carefully defined although apparently hypertension can develop in the absence of any selective change.

Cortical, neural, humoral and local reflex vasomotor activity all contribute in shaping the complex physiologic manifestations of the disease. Too little is known to assign preëminence to any one factor in this process.

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Diagnosis and Natural History of Hypertensive Vascular Disease*

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In considering the diagnosis and natural history of hypertensive vascular disease (HVD), it is essential that there be a common understanding as to the definition of this disorder. To achieve such an understanding is more difficult than might be supposed.

Ordinarily HVD is considered to be characterized by the presence of hypertension secondary to increased peripheral resistance in the arteriolar bed, other known causes of hypertension being absent. Hypertension is defined as an abnormal elevation of diastolic blood pressure. However, the normal blood pressure is determined by the composite interaction of many forces, and it is often impossible to make a sharp distinction between normal and abnormal values. Moreover, there may be periods in the course of HVD in which the blood pressure is not elevated. It must also be stressed that the rise in diastolic blood pressure, the criterion on which clinical diagnosis usually depends, represents an effect rather than a cause and is but one manifestation of the disorder.

These remarks serve to emphasize that definitions cannot be readily made until mechanisms are more clearly understood. There is no measurement more variable than that obtained by the determination of arterial tension. A discussion of the diagnosis and natural history of HVD properly begins, therefore, with an appreciation of the forces which influence the blood pressure.

NORMAL BLOOD PRESSURE[1,2,3]

The maintenance of arterial pressure is dependent upon the output of the heart per unit time and upon the blood volume, viscosity of the blood, elasticity of the larger arterial walls and the peripheral resistance offered primarily by the arterioles. These in turn may be modified by secondary regulatory mechanisms such as central and peripheral autonomic controls. The blood pressure exhibits innumerable fluctuations in which age, position, activity, obesity and particularly emotional state play an important part.

In this clinic normal "resting" blood pressure values, the lowest readings obtained on repeated examination by the same observer in a coöperative and relaxed subject lying in bed, are rarely above 120/80 mm. of mercury. Levels casually obtained are generally below 140/90. The blood pressure of children is lower than that of adults. Obesity may produce falsely high sphygmomanometric readings. Values in the 90/50 mm. range are not rare, particularly in young, asthenic individuals; in the absence of other causes of hypotension such levels should be looked upon as a constitutional variant and not as due to disease

Once maturity is reached, the blood pressure does not increase with age except as a reflection of an underlying organic change, such as arteriosclerosis of the aorta with loss of vascular elasticity. The resultant systolic hypertension, which may also be found in some patients with hyperthyroidism, aortic insufficiency or heart block when the rate is slow, should be sharply separated from those conditions in which there is elevation of the diastolic blood pressure.

The blood pressure is slightly influenced by respiration and position. Profound in-

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creases in systolic pressure may accompany exercise. Emotional influences exert marked effects, particularly upon the systolic pressure. Some hyperreactive individuals, often with autonomic nervous system imbalance, may exhibit occasional and transient abnormal elevations of blood pressure as high as 160/100 mm. of mercury and may show this tendency for transitory hypertension for months or a lifetime. Changes as great as 50 mm. of mercury systolic and 20 mm. of mercury diastolic can occur in less than one minute or two.

The arterial pressure may be further affected by underlying pathologic states unrelated to specific causes of hypertension. These include cardiac arrhythmias, arteriovenous communications, pain, fever, shock and hypofunction of the thyroid, adrenal or pituitary glands.

Unless the conditions of measurement are accurately determined and constantly maintained, analyses of normal blood pressure readings are without significance. It is more important to realize that there is a wide and variable range in normal blood pressure.

HYPERTENSION[4,5,6]

From the preceding remarks it is obvious that an overlap exists which makes a sharp differentiation between normotension and hypertension impossible. Hypertension should be suspected only if the diastolic blood pressure occasionally rises above 90 mm. of mercury. It becomes increasingly probable the more often this value is exceeded. Lability of blood pressure readings is characteristic of the early hypertensive state, is sometimes observed throughout its course and should be regarded as a true manifestation of the disorder.

The systolic blood pressure is usually increased in hypertension, but a reading of less than 140 mm. of mercury does not exclude the hypertensive state, nor does a normal blood pressure always exclude antecedent hypertension. Many hypertensive subjects have been observed in this clinic with a reduction in tension to normal or even low normal values following rest or relaxation. Periods up to three weeks are often required before minimal readings are obtained. "Resting" values in one patient (with retinitis, cardiac hypertrophy and repeated casual blood pressure determinations never recorded below 170/100 mm. of mercury) fell as low as 90/52 on hospital admission and rose promptly to original values upon discharge. Fever frequently lowers the blood pressure for days. Normotension may persist for many months after a hypertensive subject has developed a myocardial infarction or cerebral vascular accident.

DIAGNOSIS

The diagnosis of HVD rests at present on the repeated finding of hypertension when other causes of diastolic blood pressure elevation are excluded. As previously pointed out, there are obvious difficulties in many cases in deciding whether or not hypertension exists. In the absence of consistent and significant deviations from normal, time and hindsight may be required before conclusions can be reached.

Many congenital and acquired primary disorders of the urinary tract or renal circulation, particularly acute and chronic glomerulonephritis, polycystic kidneys, pyelonephritis and urinary tract obstruction, may be associated with hypertension. Other disease processes include coarctation of the aorta, hypertension in toxemia of pregnancy, adrenal and pituitary tumors, pheochromocytomata, lupus erythematosus disseminatus and periarteritis nodosa. A complete list would include many other conditions, ranging from acute hypertension of central nervous origin to carbon tetrachloride poisoning and acute porphyria, but the above comprise the more frequent disorders involved in differential diagnosis.

INCIDENCE

Mortality statistics deal with cardiovascular and renal deaths, not with hypertension alone. Hospital, industrial, military, insurance and other figures are often difficult to interpret because of varying criteria

of diagnosis, predominance of selected groups in different series, casual or single blood pressure determinations and inadequate documentation.

Among 2,000 unselected and apparently healthy men between the ages of twenty to thirty we have found repeated "resting" blood pressures consistently above 140/90 mm. of mercury in thirty-four subjects (1.7 per cent), all of whom had several negative urinalyses. In examining Robinson and Brucer's unselected group,[7] it may be noted that of 2,387 males and 1,178 females between the ages of thirty to forty, approximately 4 per cent showed diastolic values in excess of 90 mm. of mercury in the course of one thirty-minute period of observation. In a series of 10,883 persons in all age groups, about 7 per cent exhibited abnormal diastolic readings.[6] Several series report a much higher incidence, but systolic hypertension or possible labile blood pressures are rarely excluded from consideration.

In all probability the true incidence of hypertension lies between these extreme values, certainly not less than 2 per cent and probably not more than 7 per cent. It would be reasonable to assume that about 5 per cent of the adult population of the United States is afflicted with this disorder.*

HVD is said to be less evident among primitive peoples unless they are transferred to more civilized environments. Heredity is an important factor, with the majority of surveys indicating a clear-cut family history in 50 to 60 per cent. Obesity, short and stocky body types and hyperkinetic bodily reactions appear to be present more frequently in association with hypertension. Psychological types have been repeatedly described, a large percentage of subjects showing hostility and aggressive conflicts, emotional lability and anxiety patterns expressed in acute generalized reactions rather than localized or referred. "Abnormal vascular responsiveness," "hyperreactivity," and the "prehypertensive state" are terms frequently encountered. Although normotensives whose vasomotor patterns react in excess are statistically more likely to develop hypertension, hyperreactivity is not an infallible warning.

It is generally agreed that HVD is somewhat more common among women. However, it is difficult to arrive at exact ratios, as the hypertensive state is frequently recognized for the first time during pregnancy. If one chooses to group persistent post-toxemia and postpartum elevations of blood pressure with prepregnant hypertension, this disorder is about four times as common in women as in men. If one excludes all female subjects in whom the onset of hypertension and pregnancy appear to be related, a 2 to 1 or even smaller ratio results.

NATURAL HISTORY OF THE DISEASE

For reasons that have been stated elsewhere,[8] an accurate and complete picture of the natural history of HVD is not readily achieved. Varying diagnostic criteria and difficulties in obtaining an unselected series have made many reports open to criticism. There are many obstacles which prevent documentation of the disease from its incipiency, as the majority of patients seek care only after symptoms appear.

To avoid selection as much as possible, data have been secured from multiple sources. Records of 2,147 patients with established HVD were obtained from a hypertensive clinic which has operated continuously for more than twenty years, from hospital admissions, hospital personnel, student health, private practice and industrial sources. From these it was possible to select 250 subjects followed at frequent enough intervals for more detailed analysis, none of whom had received therapy other than reassurance or mild sedation. The basis of selection consisted only in the documentation of HVD (repeated diastolic blood pressure values above 90 mm. of mercury, and the exclusion of other causes of hyperten-

* Although it is common practice to record the incidence of HVD as about 25 per cent, the conclusion expressed is based on the argument that the disorder starts earlier than is generally assumed, and that the hypertension observed in older age groups includes many subjects with systolic hypertension or degenerative vascular disease. This remains a controversial subject.

sion) and a sufficient period of observation to permit complete routine studies and the elimination of subjects whose hypertension was transient. Even so, some element of selection is inherent in a study of this kind. The group of 250 patients represented primarily a clinic and hospital population; subjects who appeared for the first time with a terminal episode were obviously not included; the duration of hypertension prior to the first observation was inevitably unknown.

TABLE 1
SUMMARIZED DATA IN STUDY OF HYPERTENSIVE VASCULAR DISEASE

Total number of patients with HVD whose records were examined	2,147
Men	795
Women	1,352
Rapidly progressive or malignant hypertension	103
Total number of patients with HVD analyzed in greater detail	250
Men	85
Women	165
Living at the time the survey was made	207
Dead at the time the survey was made	43
Average age at time of diagnosis	36 years (range: 15–67)
Average period of observation	12 years (range: 2–41)
Average blood pressure at time of diagnosis	182/108 mm. Hg
Average blood pressure at time of last observation (excluding critically ill or terminal cases)	202/116 mm. Hg
Symptoms and signs observed in series of 250 cases*	
No symptoms during period of observation	14
Headaches	78
Migraine headaches	3
Retinal arteriolar irregularity or arteriovenous compression	94
Hemorrhages, exudate or papilledema	19
Hypertensive encephalopathy	2
Abnormalities of urine or renal function	35
Nitrogen retention	5
Increased cardiac area by x-ray	71
Electrocardiographic changes	86
Electrocardiographic changes indicative of myocardial damage	38
Cardiac pain	18
Myocardial infarction	9
Congestive failure	40
Cerebral vascular accidents	12

* Expressed in per cent of 250 cases.

Hence these data, summarized in Table 1, permit only general conclusions and considerable additional information must be gathered before a complete understanding of the natural history of the disorder is obtained.

Age at Onset. A few authors[7,9,10] have suggested that HVD begins at an early age.

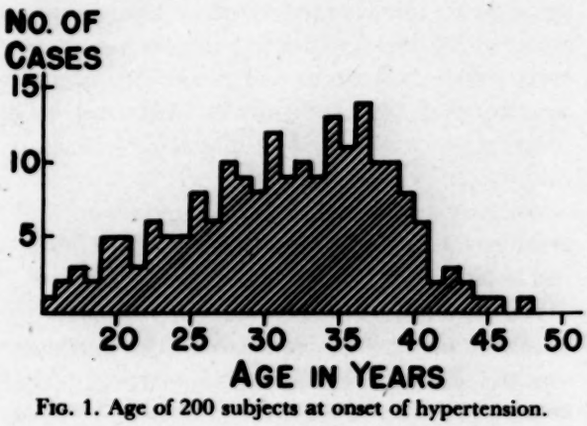


FIG. 1. Age of 200 subjects at onset of hypertension.

This is in contrast to the general acceptance of the view that the disorder is primarily "a disease of the declining years."[6] The present study supports the contention that HVD usually becomes apparent in youth and early adult life.

It was possible to establish the age at onset of hypertension in 200 subjects by the documentation of HVD and its sequelae following a period of known normal blood pressure. Normotensive criteria included multiple normal blood pressure determinations in individuals not on bed rest or in the hospital and not obtained during convalescence from acute or febrile illness. Hypertensive criteria included multiple readings greater than 140/90 mm. of mercury, at least three negative urinalyses, no clinical evidence of other causes of hypertension and onset not in association with pregnancy. All subjects were followed for at least two years, with ultimate development of at least one objective hypertensive complication. The series was obtained by examination of the 2,147 hypertensive records mentioned above, all of individuals at least seventeen years of age at the time of final observation, 50 per cent over the age of forty, and 17 per cent ranging in age from

fifty-five to eighty-six. The age at which hypertension was first manifest was recorded even though the last normotensive observation frequently preceded this point by periods as long as five years.

The data (Fig. 1) indicate that the onset of hypertension invariably occurred in subjects under forty-eight years of age, all but sixteen (92 per cent) being under the age of forty. The failure to demonstrate the appearance of hypertension in older subjects in no way excludes the possibility that it may occur at any age.

Sex. There were 1,352 women and 795 men in the entire series, a 3 to 2 ratio favoring women.

Duration of Life. The average period of observation in the group of 250 patients studied in detail was twelve years. In the selected series in which the onset of HVD could be documented the average period of observation was fifteen years. Long survival (more than twenty years), often with comparative well being, was not a rarity. One woman, still in reasonably good health, had had definitely established and repeatedly recorded hypertension for more than forty-one years.

It is well established that HVD and its sequelae reduce life expectancy and may cause death within a period of months from the time of diagnosis, but a survey of the 2,147 hypertensive records indicated that in only 5 per cent could the diagnosis of malignant hypertension be entertained. As the majority of records studied indicated well established disease when first seen, and as the majority are still living, it must be emphasized that average life expectancy is undoubtedly longer than generally assumed and, if anything, longer than these figures would indicate.

Symptoms. HVD may be present for many years without symptoms. The majority (86 per cent) of patients complained of fatigue, weakness, nervousness, dizziness, palpitation, insomnia or headaches at some time in the course of their disease. Evidence of autonomic instability was not infrequent. It must be recalled, however, that some of these symptoms are not uncommon in the general population.

Headaches (78 per cent*) were usually of minor degree and even the more intense headaches were inconstant and often disappeared completely after months or years of great severity. They were usually occipital, generalized or over the vertex, more apt to be present on awakening or in the morning and on occasion (3 per cent) assumed a typical migraine pattern in subjects with no familial or previous history of idiopathic migraine. The frequency of headaches as a complaint in normotensive individuals and occasional encounters with headaches due to other causes, make it advisable to consider other etiologies rather than to attribute them routinely to the hypertensive state.

Blood pressure: Although there was considerable variation in individual cases, the general tendency of the blood pressure was to increase but slowly throughout the years of observation.

Retinopathy: Retinal abnormalities were common in the group of 250 patients studied, and eventually included arteriolar irregularities and arteriovenous compression (94 per cent), hemorrhages, exudate or papilledema (19 per cent). In rare cases even severe retinitis showed conspicuous regression. Intermittent spasm of retinal vessels could sometimes be seen on ophthalmoscopic examination. It was found wholly impractical to classify hypertension according to the degree of retinitis; even malignant hypertension could appear without significant retinal change.

Hypertensive Encephalopathy. In patients with marked hypertension or in the rapidly progressive malignant phase of their disease, acute recurrent attacks of convulsions, headaches, vomiting, mental changes, transitory paralyses and the like may occur (2 per cent).

Arteriolar Nephrosclerosis. In the series studied, about one-third of the hypertensive group eventually exhibited some renal

* Percentage figures refer to the 250 hypertensives in whom detailed analyses were possible.

abnormalities in the form of relative polyuria, nocturia, diminished concentration power and albuminuria, with or without the presence of urinary red cells and casts. Tests indicating progressive glomerular and tubular damage accompanied these findings. Nitrogen retention developed in 5 per cent.

It must be kept in mind that not all the renal findings need be on the basis of arteriolar nephrosclerosis alone. At times renal arteriosclerosis may contribute to the picture, and reduced renal blood flow secondary to congestive failure may be an additive factor.

Hypertensive Heart Disease. Evidence of an increased cardiac area by x-ray (primarily enlargement of the left ventricle) was obtained in 71 per cent. As compared with other pathologic changes in HVD, cardiac hypertrophy was conspicuously absent in some cases even after long-sustained hypertension. There is accumulating evidence that cardiac hypertrophy can scarcely be attributed only to the elevation of blood pressure, arteriosclerosis or to the work of the heart. Congestive failure may occur with no demonstrable coronary artery disease subsequently revealed at autopsy.

Accentuation of the second aortic sound, apical and aortic systolic murmurs and occasional split sounds were frequently recorded. Electrocardiographic changes consisting of left axis deviation and left ventricular strain patterns appeared in the majority of patients.

ARTERIOSCLEROTIC VASCULAR COMPLICATIONS

It may be debated as to whether degenerative alterations in arteries are augmented by the hypertensive state or are merely coincidental. The frequency of coronary artery disease, cerebral vascular accidents and peripheral vascular changes among hypertensives, as well as comparative analyses of autopsy material, favor the former interpretation. No consistent relationship of any of these complications to blood pressure levels or duration of the disorder could be established.

Coronary artery disease: Cardiac pain was a complaint in 18 per cent of the patients at some time during their course. Myocardial infarction occurred in 9 per cent and electrocardiographic changes indicative of myocardial damage developed in 38 per cent. Manifestations of congestive failure appeared in 40 per cent, but it must be recalled that hypertrophy alone, as well as coronary artery disease, may be associated with failure.

Cerebral vascular accidents occurred in 12 per cent of the patients in this series, often in the form of hemorrhage resulting in death, but at times in the form of multiple thrombotic episodes.

In addition to cerebral hemorrhage, epistaxes and menorrhagia are not uncommon in hypertension, and subcutaneous, pulmonary, subarachnoid, gastrointestinal, renal and adrenal hemorrhages have been reported.

MALIGNANT HYPERTENSION

This term is applicable to rapidly progressive HVD and is associated with necrosis of the arteriolar walls, advanced hyalinization and petechial hemorrhages superimposed upon the arteriolosclerotic picture, involving particularly the kidneys and retinae. Although malignant hypertension was on occasion apparent at the onset, it was more apt to develop without warning among patients who previously exhibited a mild and static course. The majority exhibiting this phase were males. The diagnosis of malignant hypertension appeared probable in 5 per cent of the over-all series of 2,147 patients.

PROGNOSIS

In analyzing this series, nothing appeared to alter the impression gained in the study of a selected group.[8] In general, the initial height of blood pressure, headaches and other symptoms, cardiac hypertrophy and retinal changes without retinitis bore no relationship to ultimate outlook. Progressive rise in blood pressure, cerebral vascular accidents, retinitis, coronary artery disease,

congestive failure or albuminuria indicated a relatively poor prognosis though with notable individual exceptions.

CAUSE OF DEATH

Death in HVD is due chiefly to arteriosclerotic complications. The data in this series are too few to be significant, but figures from the literature indicate that congestive failure (40 to 50 per cent), myocardial infarction and cerebral hemorrhage (each 10 to 20 per cent) are leading causes with not more than 5 per cent dying of renal insufficiency.

CONCLUSIONS

Measurement of the blood pressure is at best rough and variable. A sharp differentiation between normotension and hypertension is impossible. Although high blood pressure is but a manifestation of HVD, the clinical diagnosis rests on the repeated finding of hypertension when other causes of diastolic blood pressure elevation are excluded. It should be emphasized that systolic hypertension alone must be separated from those disorders in which the diastolic blood pressure is affected, and that a normal blood pressure may be recorded in the course of HVD under certain physiologic and pathologic conditions.

HVD is a common disorder, the first signs of which usually appear in youth and early adult life. The course of HVD is extremely variable, with gradations from a benign, asymptomatic form to cases of malignant hypertension with a rapidly fatal outcome. Average life expectancy is, however, considerably longer than is generally assumed.

The symptoms, signs, complications and outlook are dependent upon associated autonomic instability, arteriolosclerosis, hypertensive heart disease, and arteriosclerotic changes. These alterations are frequently but not invariably present, differ in their intensity and points of maximal attack and are not related to the level of the blood pressure or to the duration of the disease.

Considerable additional data must be gathered before complete information concerning the natural history of HVD is obtained.

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Conference on Therapy

Treatment of Pneumonia

These are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. WALSH MCDERMOTT: This conference will be on the management of pneumonia. The discussion will be opened by Dr. Tompsett.

DR. RALPH TOMPSETT: The therapeutic aims in the treatment of pneumonia are: first, to control the infection, second, to promote the patient's comfort and third, to manage or, if possible, prevent the development of irreversible anatomic or physiologic changes during the period required for the control of the infection. Accomplishment of these aims requires the use of specific antimicrobial agents chosen on the basis of the etiology of the disease in the particular patient and certain general measures which are useful in pneumonia regardless of etiology. In no case may either the specific or the general measures be neglected. The need for many of the general measures, however, is considerably reduced in those forms of pneumonia for which potent antimicrobial agents are available.

The most successful use of penicillin, streptomycin and sulfonamides in pneumonia requires accurate bacteriologic diagnosis. Consideration of the present situation, however, makes it quite evident that the physician must do a great deal of work to discover a relatively few patients for whom potent antimicrobial agents other than penicillin are available. As you know, probably over 95 per cent of all the patients with primary pneumonia will be found either to have pneumococcal pneumonia or primary atypical pneumonia. If penicillin is given to all of these patients purely on the basis of the diagnosis of pneumonia without regard to etiology, most of the patients will be receiving as effective an antimicrobial agent as is available. Some of them who have primary atypical pneumonia, will not be helped by the drug but very little, if any, harm will be done.

Thus, efforts made to arrive at a precise bacteriologic diagnosis are directed toward the detection of a relatively small number of cases, the most important of which are those caused by Friedländer's bacillus and tubercle bacillus. It is important that these cases be detected early because the serious damage which may occur within a short time may often be prevented by correct therapy.

In pneumococcal pneumonia, the commonest form of pneumonia aside from those occurring in epidemics, the most effective agent for the control of the infection is penicillin. The dosage of penicillin generally employed is approximately 20,000 units dissolved in 1 cc. of saline solution, given intramuscularly every three hours. Larger doses may be used if it is desired to lengthen the interval between injections. Equally satisfactory results may be obtained by the use of penicillin orally in doses of 100,000 units every two hours.

A variety of vehicles have been proposed for the administration of penicillin in an attempt to delay its absorption and thus obviate the necessity for repeated injections. One preparation, the "Romansky formula" of penicillin in oil and beeswax, has received extensive clinical trial. With this preparation it is possible to treat patients with pneumococcal pneumonia using only one

or two daily injections of 300,000 units of penicillin. Recently liquid preparations of this material have become available and these have done away with some of the disadvantages of the earlier preparations.

Therapy of pneumococcal pneumonia by any of these regimens should be continued for a minimum of seven days and preferably for ten days. With this treatment many patients with pneumococcal pneumonia may be expected to have a crisis within twenty-four hours, and in the vast majority within forty-eight hours. In the remainder of the uncomplicated cases by the end of the forty-eight-hour period there will be definite evidence of improvement but the defervescence may be less abrupt. In some, after this initial period of defervescence, there follows a period of secondary low grade daily fever which may persist for as long as a week, although not accompanied by other evidence of toxemia. Failure to obtain a response to penicillin therapy in the form of one or another of the patterns which I have described constitutes strong evidence that some complication is present, or that the pneumonia is not caused by pneumococcus.

The various methods of administration of penicillin I have mentioned have been notably satisfactory in pneumonia. All of them involve an attempt to maintain "continuously effective" antimicrobial concentrations of penicillin in the body which experience has shown are very effective. It has also been shown that it is not necessary to maintain continuously high concentrations. The studies of Tillett and his associates have shown that satisfactory results may be obtained in the treatment of pneumococcal pneumonia with the use of doses of only 10,000 to 25,000 units of penicillin in saline, given three or four times a day. It was further shown by these workers that equally satisfactory results were obtained when some of the intervals between doses were twelve to sixteen hours. Other clinical studies have shown satisfactory results with dosage regimens which could not possibly have maintained what were previously considered "therapeutic levels" for more than twelve to fifteen hours in each day. During the past seven months we have treated twenty-six patients with pneumococcal pneumonia, employing injections of aqueous solutions of penicillin, 300,000 units each, at intervals of twelve to twenty-four hours. It has been our practice to give a dose of 300,000 units as soon as the diagnosis is made. Then the patient is given 300,000 units at 8:00 A.M. and 8:00 P.M. until it is seen that defervescence is occurring. At this point, the regimen is changed to only one injection of 300,000 units a day, at 8:00 A.M. The results in these twenty-six patients, as judged by all the usual criteria, have been identical with those of other treatment regimens.

There are two other forms of pneumonia in which the same principles of penicillin therapy are applicable. These are streptococcal and staphylococcal pneumonia. It is possible that streptococcal pneumonia occurs fairly frequently in a mild form following pharyngitis and, if so, it closely resembles atypical pneumonia. This is not the same entity as the well known streptococcal pneumonia in which there is a widespread involvement of the lung, with all the manifestations of a severe infection and rapid development of empyema, bacteremia and metastatic abscesses. It appears that satisfactory results may be anticipated in this severe form of streptococcal pneumonia with the use of penicillin, provided therapy is instituted early enough and before irreversible anatomic or physiologic changes have occurred. In these cases it may be well to use the agent in dosage two or three times as high as that used in pneumococcal pneumonia.

Staphylococcal pneumonia is also rare. Most of the experience has been gained in those cases which occur in association with epidemics of influenza. The same general principles apply as with streptococcal pneumonia. The penicillin dosage should be even larger for, although many strains of staphylococci are highly sensitive to penicillin, there is considerable variation among freshly

isolated strains. Virtually all cases, however, may be expected to be favorably influenced by large doses of penicillin.

The second most frequent type among the bacterial pneumonias is that caused by Friedländer's bacillus. Although these cases make up only a small proportion of all the pneumonias, they constitute a particularly important group today because they are not influenced by penicillin, whereas they respond favorably to streptomycin and the sulfonamides. The recognition of cases of Friedländer's pneumonia is made even more important by the fact that all too frequently their progression is rapid; within a day or two of the time the patient presents himself to the physician, the stage of abscess formation is reached. Experience with Friedländer's pneumonia indicates that the treatment of choice is the combined use of streptomycin and a sulfonamide. The organisms are generally sensitive to streptomycin. Many of the strains are also susceptible to sulfonamides. Despite the fact that in many of the patients treated with streptomycin alone the results have been satisfactory, there is theoretical reason, supported by many *in vitro* studies, to believe that the combined use of the two drugs may prevent or postpone the emergence of organisms resistant to streptomycin. The average dose of streptomycin is 40 mg. per Kg. daily or about 2.0 Gm. per day in the average patient, given in three or four fractions by intramuscular injection. The usual dose of the sulfonamides is used; for example, 2 Gm. of sulfadiazine as the initial oral dose, followed by 1 Gm. every four hours.

Another form of pneumonia which may be of acute onset and which may very closely simulate the more usual varieties is tuberculous pneumonia. This may also progress rapidly to the stage of irreversible or incompletely reversible damage. Consequently, early recognition of the etiology is of the utmost importance. Here also, early use of streptomycin offers the best possibility for reversal of the inflammatory process. The daily dosage of streptomycin is somewhat smaller than in the case of Friedländer's infection because the treatment is more prolonged.

The general measures, namely, those of keeping the patient at rest during the acute phase of the pneumonia, relief of pain with codeine or morphine and the use of oxygen therapy may all be necessary. They have less importance in those cases in which effective antimicrobial agents are available. In some cases, such as the primary atypical pneumonias, they may be the only type of therapy available. Such supportive measures are very helpful in these cases, as well as in other forms of pneumonia with complications and in those who come under medical care only after the disease is in the advanced stage.

DR. MCDERMOTT: As Dr. Tompsett said, the two important features in the management of pneumonia are the proper use of antimicrobial therapy and the institution of the general measures mentioned. In most patients with bacterial pneumonia these general "supportive measures" are no longer of great importance. In the other large group of pneumonias, identified by the clinical syndrome of primary atypical pneumonia, the general measures may be of prime importance since no antimicrobial therapy is available.

We are fortunate today in having with us Dr. Frank Horsfall and Dr. Harold Ginsberg of the Rockefeller Institute. We promised that we would not call on them for any formal presentation but they are available for questions. I might start by asking them some questions on atypical pneumonia. As you know, however, these gentlemen have not limited their studies to atypical pneumonia and we may take advantage of their presence by questions on other aspects of pneumonia as well.

Dr. Horsfall, I would like to ask you about a question which is repeatedly discussed on the service: Can one be sufficiently certain of the diagnosis of the clinical syndrome of primary atypical pneumonia to justify withholding antimicrobial therapy for, let us say, a forty-eight-hour period, or should all patients with an acute pneumonia receive

antimicrobial therapy for a trial period with the view in mind that the response will help to establish the diagnosis of atypical pneumonia?

DR. FRANK HORSFALL: It would seem to me that in the large majority of patients with primary atypical pneumonia a careful clinical examination, including a white blood cell count, ought to make it possible to conclude that the disease is probably not bacterial pneumonia. There is a fairly sharp difference between the majority of patients with primary atypical pneumonia and the majority of patients with bacterial pneumonia. Physicians who are accustomed to seeing pneumonia should, in the majority of instances, have no great difficulty in differentiating one from the other.

As to the second half of your question, if one is reasonably sure that the diagnosis is primary atypical pneumonia, it seems to me not only unnecessary but indeed unwise and poor medicine to give a therapeutic agent which has no effect on the disease merely for the purposes of security.

DR. HARRY GOLD: Would Dr. Tompsett state how he makes fairly certain that the pneumonia is the primary atypical variety? What are its diagnostic characteristics, and especially the decisive ones?

DR. TOMPSETT: One can be fairly certain of the diagnosis of primary atypical pneumonia only by careful evaluation of several features of the disease in comparison with similar features of bacterial pneumonia. In primary atypical pneumonia, the onset is generally less acute and the symptoms are less severe than at the same stage of bacterial pneumonia. Chest pain is less likely to be prominent. The cough may be distressing but is often not productive of much sputum and the sputum is not likely to be bloody or rusty in the early stages. The white blood cell count is generally between 5,000 and 10,000 per mm.^{3} and although it may be higher, it rarely goes as high as one generally finds it in the bacterial pneumonias. Those are the chief features. It should be emphasized, in connection with the white cell count, that patients with very severe bacterial pneumonia may not have a leukocytosis and may even have counts below 5,000. These cases, however, are not the ones in which confusion arises.

DR. MCDERMOTT: The notion has been advanced that the administration of antimicrobial therapy might prevent a so-called secondary infection in these patients. Has secondary infection been a problem in primary atypical pneumonia?

DR. HORSFALL: Secondary infections in primary atypical pneumonia are exceedingly rare. Their incidence is certainly not greater than 1 in 200. When they occur, they can be recognized at once and that is not too late for successful antibacterial therapy. To give 199 patients frequent injections in the hope of preventing bacterial infection in one, seems to me unnecessary and overzealous treatment.

DR. MCDERMOTT: I have never seen bacterial infections following the atypical pneumonias we encounter here.

DR. HORSFALL: It does happen but it is rare.

DR. MCDERMOTT: Dr. Tompsett said something about mild forms of bacterial pneumonia, such as streptococcal pneumonia with which we are all familiar. Such cases might resemble atypical pneumonia. Have you any thoughts on that point?

DR. HORSFALL: I agree with what Dr. Tompsett has said and, indeed, I will go one step further. We have seen patients in whom we did not suspect bacterial pneumonia but who, on careful study, proved to have had pneumococcal pneumonia. The clinical findings, the x-ray and even the leukocyte count strongly suggested that the infection was primary atypical pneumonia. Finally, when all the serologic and other laboratory work was completed, it became evident that it was not the correct diagnosis, and that the patient actually had pneumococcal pneumonia due to a specific type of pneumococcus and showed a specific antibody response. But this is a rare occurrence and such cases do not constitute a therapeutic problem because they are so mild.

DR. MCDERMOTT: That brings up another problem. It is virtually impossible now to obtain diagnostic sera for the typing of pneumococci in sputum. What do you think about the necessity or the clinical usefulness of typing sputum?

DR. HORSFALL: That is an exceedingly difficult question to answer and particularly difficult for me. It would seem to me that there is little clinical usefulness in typing pneumococci at the present time. Indeed, some of the best clinics in this city, and in others, carry out very effective therapeutic regimens in pneumococcal pneumonia and unfortunately have no idea with what types they are dealing. Manifestly, one can, if necessary, handle the therapy of pneumococcal pneumonia satisfactorily without knowing the type.

DR. MCDERMOTT: I agree, but I believe that typing is still of very great importance. To be sure, pneumococcal pneumonias can be treated successfully without diagnosis of the type. But there remains the small number of bacterial pneumonias which require specific antibacterial agents not used in pneumococcal pneumonia. It is, therefore, essential to establish the diagnosis of pneumococcal pneumonia and typing seems to me the quickest way of recognizing that group. If one finds a Type I or Type II, or if one is able to recognize the pneumococcus by direct typing, it is fairly convincing evidence that the patient has pneumococcal pneumonia and not one of the other bacterial pneumonias. Would you agree to that?

DR. HORSFALL: No, not entirely.

DR. MCDERMOTT: You would not?

DR. HORSFALL: Unfortunately, no. I agree with most of what you have stated regarding the advantages of typing. But it seems to me that to make a diagnosis of pneumococcal pneumonia, one must have more evidence than the fact that a certain type of pneumococcus is present in the sputum. If it turns out to be Type I or Type II, I agree that the evidence is fairly decisive; but if the higher types, including III, V, VII, VIII, XIV and others are discovered, it is uncertain that the pneumonia is due to the pneumococcus.

DR. MCDERMOTT: I would agree that the higher types leave one uncertain. Would you agree that direct typing is a quick means of establishing the fact that pneumococci are present in the sputum? The interpretation of the finding in relation to the etiology of the disease is, to be sure, another matter. Direct typing of sputum at least shows pneumococci are there and might possibly be the cause of pneumonia.

DR. HORSFALL: I would agree to that.

DR. MCDERMOTT: Dr. Ginsberg, how long should patients with atypical pneumonia remain in bed? We have seen relapses and we were quite impressed with the studies during the war which indicated that relapses were frequent when the patients were allowed up too early.

DR. HAROLD GINSBERG: The general criteria which have been set up in our own hospital and in others are as follows: The patient should not be up and about as long as there is fever or a fair number of crepitant râles. In a small number of patients a very few dry fine râles may be heard during the early part of convalescence which disappear faster if the patient is allowed some activity. I strongly believe that x-ray finding of consolidation should not alone be a factor in keeping a patient in bed.

DR. MCDERMOTT: But they should be kept in bed if they have physical signs?

DR. GINSBERG: Yes, they should be when there are physical signs. We all know that patients may show areas of consolidation by x-ray which last as long as two or three months and sometimes longer. Those patients may be returned even to full activity. In the Army it was quite common to send such patients to reconditioning centers and allow them full activity there.

DR. MCDERMOTT: With roentgenologic but no other evidence of pneumonia?

DR. GINSBERG: That is correct.

DR. MCDERMOTT: But not with physical signs?

DR. GINSBERG: No, not with physical signs. In the separation centers it was a

common practice to have patients sent to the hospital because they showed x-ray signs, never having had a physical sign or symptom. Full activity has never been shown to be harmful in those patients.

DR. MCDERMOTT: Do you believe that premature activity predisposes to relapse?

DR. GINSBERG: Yes, I do.

DR. MCDERMOTT: Do you find the sedimentation rate of any value?

DR. GINSBERG: I think that often the sedimentation rate is down to normal while they still have abnormal physical signs and in that case I would not allow them unlimited activity.

DR. MCDERMOTT: I take it that you allow these patients to be up and about when the fever has subsided even though they show râles of a particular type? Have you any idea why they tend to relapse if you allow them unlimited activity too soon?

DR. GINSBERG: No. I am not even sure it is so although it seems to be. What do you think, Dr. Horsfall?

DR. HORSFALL: I do not know of any evidence which proves that they relapse more frequently when they are allowed up in the presence of physical signs. Nonetheless, it seems to me wise to keep them in bed when signs are present.

DR. MCDERMOTT: Dr. Muschenheim, would you agree with Dr. Tompsett's statement that tuberculous pneumonia can mimic an acute bacterial pneumonia or the atypical pneumonia?

DR. CARL MUSCHENHEIM: I think it is much more likely to mimic atypical pneumonia than bacterial pneumonia, particularly because the white blood cell count is so frequently normal or only slightly elevated in both atypical pneumonia and tuberculous pneumonia. In fact, I think one of the most difficult differential diagnoses in pneumonia is that between primary atypical pneumonia and tuberculous pneumonia. As Dr. Tompsett has pointed out, this differential diagnosis is of increasing importance now that we have an effective treatment for tuberculous pneumonia.

DR. MCDERMOTT: Perhaps you are not as apt to use chemotherapy in those tuberculous pneumonias which resemble atypical as in those which resemble the other bacterial forms. In other words, you might not want to give streptomycin immediately to a patient who had just a small patch of consolidation, whereas you probably would start streptomycin therapy at once in the patient with involvement of an area as large as two-thirds of a lobe or a whole lobe.

DR. MUSCHENHEIM: It is not uncommon in atypical pneumonia to have large areas of consolidation.

DR. MCDERMOTT: In the extensive tuberculous pneumonias that involve most or all of a lobe with an acute exudative process, how difficult is it to demonstrate tubercle bacilli in the sputum?

DR. MUSCHENHEIM: Sometimes it is quite difficult. I think most failures are occasioned by not looking for them right away. Often the diagnosis is not even considered at first. They are frequently confused with the other bacterial pneumonias and the diagnosis is not thought of until there is a failure of response to penicillin or sulfonamide. Then, in other cases thought to be primary atypical pneumonia, tuberculosis is not considered until weeks have passed in which the presumed atypical pneumonia has failed to improve as anticipated.

DR. MCDERMOTT: It should be possible then to demonstrate tubercle bacilli readily?

DR. MUSCHENHEIM: In the early stages one or two negative sputum examinations are sometimes obtained but one or two negative sputum examinations for acid-fast bacilli certainly do not even rule out the diagnosis.

DR. MCDERMOTT: I do not wish to ask all the questions. Are there other questions now?

DR. MCKEEN CATTELL: I have one for you, Dr. McDermott. A year or two ago you accumulated some pretty convincing evidence showing that the high peak concentrations are not important in relation to penicillin therapy. I am wondering whether

this new schedule of doses at twenty-four-hour intervals does violence to that idea?

DR. MCDERMOTT: I think it is impossible to say, Dr. Cattell, because no one really knows whether or not the high peaks of penicillin concentration above a certain point serve a useful purpose. It is suspected that the high peaks do not serve a useful purpose. One of the main reasons for suspecting this is the notable efficacy of the penicillin-beeswax preparations in which peaks are seldom obtained. In evaluating the type of intermittent therapy we have employed one must consider two features of the penicillin concentrations: first, the intramuscular administration of 300,000 units of aqueous penicillin produces a very high concentration of penicillin in the circulating blood within a few minutes; second, it also results in the maintenance of penicillin concentrations above a certain minimum level for a fairly long period of time. We believe that the "effective concentration" of penicillin in the body is not known. It is generally assumed that in a particular infection there is a certain "effective concentration" of penicillin at the site of infection. Presumably, concentrations below this are ineffectual and increments above that value are of no added benefit. Obviously, for successful therapy in acute infections it is necessary to maintain "effective" antimicrobial action for some period during each twenty-four hours. The length of that period, whether it be four hours or twenty-four hours, probably depends on the speed with which that particular bacterial species multiplies and produces pathologic changes. Dr. Tillett's work, which has been amply confirmed by numerous investigators, would indicate that in pneumococcal pneumonia one has only to maintain the minimum detectable concentration of penicillin for about six hours out of the twenty-four and the regimen Dr. Tompsett has been using provides just about that by a single injection of 300,000 units of aqueous penicillin daily.

DR. CATTELL: What concentration do you regard as an effective one in pneumococcal pneumonia?

DR. MCDERMOTT: We do not know. We suspect that it is less than the minimal detectable concentration which is approximately 0.08 units per cc. of serum with the method of assay we use. In staphylococcus infections the effective concentration is higher.

DR. GOLD: Do you regard a period of time below this presumed "effective concentration" in the blood as an important feature in therapy? That is to say, do you aim to supply the drug in such a way as to provide, first, a high peak, then a plateau of an "effective concentration" and finally, a period below an "effective concentration" as a means of making the organisms more amenable to reason?

DR. MCDERMOTT: I do not think we can carry it quite that far, Dr. Gold. The original purpose of intermittent therapy was merely for convenience. There is evidence in one particular infection that one form of humoral immunity to the infection is much less interfered with by intermittent therapy than by continuous therapy. This observation may have no great significance in acute bacterial infections such as those caused by streptococci and pneumococci. It would have considerable practical value if the same general principle prevailed in the more chronic infections, such as tuberculosis, syphilis and staphylococcus infections. In other words, it is at least possible that the development of acquired immunity might be less suppressed by intermittent than by continuous therapy. It is an important question at the moment but there is very little evidence available concerning it.

DR. GINSBERG: One question comes to my mind along these lines. Since we are looking for a convenient and efficacious agent which will maintain continuous blood levels, perhaps it has been a mistake virtually to remove the sulfonamides from the armamentarium of the physician. It is practically not employed any more. Perhaps it is con-

sidered old fashioned. When properly used it is an effective agent, probably just as good as penicillin in pneumococcal and streptococcal pneumonia.

DR. MCDERMOTT: It is an effective antimicrobial agent but I believe that its declining use is correct. The administration of aqueous penicillin is, after all, a fairly simple matter, as are also the more fluid preparations of penicillin in oil and beeswax. Another preparation, procaine penicillin, which is now under investigation, looks extremely promising, indeed much more promising than penicillin in oil and beeswax, provided it turns out to possess no significant toxicity. I think we are right in abandoning sulfadiazine because of its toxicity and relatively low antimicrobial potency. Do you agree with that, Dr. Horsfall?

DR. HORSFALL: I do not disagree. However, for the practitioner in the home the use of a form of penicillin requiring injection is a serious problem. This difficulty can be circumvented by increasing the dosage fivefold and giving the material by mouth.

DR. MCDERMOTT: The use of sulfadiazine, as Dr. Ginsberg suggested, might partially solve the problem of Friedländer's pneumonia. All too often, cases of Friedländer's pneumonia admitted to the hospital go without a correct diagnosis during the first forty-eight hours, despite the fact that we have every facility with which to make it and there is sufficient awareness that such a condition exists. The organism is a diplobacillus which can look very much like a pneumococcus if one is examining a sputum smear at three o'clock in the morning. I believe that the difference between an excellent result and a chronic illness is probably determined in that first forty-eight hours. Would you agree to that?

DR. HORSFALL: Without any doubt.

DR. MCDERMOTT: During that period too many of our patients receive penicillin therapy.

DR. WALTER MODELL: I think you have answered my question in part. I want to know how you treat patients with pneumonia prior to making the specific diagnosis. How would you treat patients with pneumonia if you had no facilities for making a specific diagnosis?

DR. MCDERMOTT: If we had absolutely no facilities for making a specific diagnosis and there were no prospects of such within the next forty-eight hours, it would undoubtedly be safer to use sulfadiazine which at least might have some effect in Friedländer's pneumonia.

DR. MODELL: How long would you wait before you added another drug?

DR. MCDERMOTT: If you had more than one drug and no diagnostic facilities, the thing to do would be to give both penicillin and sulfadiazine. You would then be covering all the bacterial pneumonias except tuberculous. This is, however, an extreme situation. Despite the fact that we often talk of practicing medicine in isolated areas with no diagnostic facilities, those areas are becoming rare. It is possible to obtain diagnostic facilities within a seventy-two-hour period in most places.

INTERNE: We have seen patients with pneumonia caused by an organism susceptible to penicillin but who do not seem to respond to penicillin therapy. On examination it does not appear that any complicating factors are present. How long would you be willing to continue with penicillin alone, before concluding that it was ineffectual and that you had better switch to another drug like sulfadiazine?

DR. MCDERMOTT: It is a general problem in the management of pneumonia, namely, the patient who apparently has a bacterial pneumonia and who has received an antimicrobial agent but is not improving satisfactorily. Failure to respond may be usually suspected by the course during the second twenty-four-hour period. Certainly by the end of forty-eight hours, if the patient is just as ill as he was at the beginning, it is clearly apparent. Almost invariably that situation is not the result of the fact that an organism of a species usually sensitive to the drug is, for some peculiar reason, not sensitive to it in that patient. Generally, it is either not

pneumonia or one has made the wrong etiologic diagnosis of the pneumonia. For example, one may be treating Friedländer's pneumonia with penicillin. More commonly, in bacterial pneumonia some complication of the pneumonia is present, such as empyema or meningitis. Would you agree with that, Dr. Horsfall?

DR. HORSFALL: Yes, entirely.

DR. MUSCHENHEIM: In that connection, Dr. McDermott, it seems to me that the suppurative pneumonias are also ones which we always have to consider. These are of increasing importance since the prognosis in bacterial pneumonias has improved so much. An important problem in the differential diagnosis and management of pneumonia is that of making sure that there is no serious underlying primary disease like carcinoma, or that it is not a suppurative pneumonia or an early lung abscess.

DR. MCDERMOTT: By "suppurative" pneumonia, do you mean a pneumonia breaking down into an abscess, either because of the nature of the pneumonia or as a result of some anatomic distortion?

DR. MUSCHENHEIM: It may be due to mixed infection.

DR. MCDERMOTT: Would you tell us how you think you can distinguish them?

DR. MUSCHENHEIM: The response to treatment helps. The suppurative pneumonias may respond with defervescence and clinical improvement but the response may be only partial. It is not necessarily a complication of a primary pneumonia. It is a primary disease in which suppuration occurs, such as the suppurative pneumonias so commonly associated with carcinoma.

DR. MCDERMOTT: We have been impressed with the fact that, in cases of empyema complicating primary pneumonia, penicillin makes the patient look and feel better. There is some improvement but conspicuous improvement does not occur until the empyema is discovered and drained. Is that the case in suppurative pneumonias?

DR. MUSCHENHEIM: Yes.

DR. MCDERMOTT: Dr. Tompsett mentioned the antimicrobial therapy of streptococcal pneumonia and we talked about mild forms. Dr. Horsfall, have you any notion as to what we could accomplish with antimicrobial therapy today if we were faced with a pandemic of streptococcal pneumonia of the sort which was seen during World War I?

DR. HORSFALL: That is a very important question. I have heard it discussed by many people who had an opportunity to see hundreds of patients during World War I and it is their belief that present antimicrobial therapy might fail because of the time factor. A large proportion of patients who developed secondary bacterial pneumonia during the pandemic had such fulminating disease that there would have been no opportunity for the administration of adequate antimicrobial therapy. However, in those whose illness developed more slowly, I should think that the result might be exactly what one would expect now in primary bacterial pneumonias.

DR. MCDERMOTT: That brings us to another point which is disturbing me a great deal. Many of the failures of current antimicrobial therapy in pneumococcal pneumonia are of that same type. The patient comes into the hospital late in a state of cardiovascular collapse which resembles a state of shock. He succumbs despite our best antimicrobial therapy, even though it is sufficient to inhibit bacterial growth to a point at which one is unable to obtain a positive culture. I am familiar with Dr. Stead's work which showed that the mechanism of that type of shock is different from the shock which occurs through blood loss or trauma and that there is no point in attempting to treat the shock of pneumonia as one would treat surgical shock. Have you any thoughts on that?

DR. HORSFALL: Yes, I have. We have treated or attempted to treat the peripheral vascular failure which so commonly precedes the fatal issue in pneumonia and have employed the measures generally used in

surgical shock. In all honesty, we accomplished nothing but to hasten the fatal issue. Certainly, we were never able to reverse it.

DR. MCDERMOTT: You are referring to patients with a form of pneumonia which would be susceptible to antimicrobial treatment, provided you could reverse the shock. That is a very important point. We use antishock measures in these cases. The available studies, including Dr. Horsfall's own observations, however, indicate that they probably are of little or no value.

DR. GOLD: I wonder whether we could hear a little more about procaine penicillin from Dr. Tompsett. It is an interesting material.

DR. TOMPSETT: I will be glad to tell what little I know about it. Procaine penicillin is a crystalline salt formed from procaine hydrochloride and crystalline sodium penicillin G, which is relatively insoluble in water. There are several clinical investigations now in progress. The salt is put up in sesame oil or peanut oil which are, as you know, easily administered fluid preparations. It is thought that an insoluble salt of penicillin should be more slowly absorbed and hence provide more prolonged blood levels with a given amount of penicillin. This particular preparation, by all the means we have for evaluating it, looks exceptionally good thus far. As you know, a good preparation of penicillin in oil and beeswax will, after a single dose of 300,000 units, produce measurable blood levels for eighteen hours in approximately 75 to 90 per cent of patients and for twenty-four hours in about 50 or 60 per cent of patients. Thus far, with a similar dose of procaine penicillin, 100 per cent of patients had measurable blood levels for eighteen hours; 85 to 90 per cent for twenty-four hours; approximately 60 per cent or more at thirty and thirty-six hours and a significant number for as long as forty-two hours. In rare instances, measurable levels persisted for forty-eight hours. That for a single dose of 300,000 units looks good!

DR. MCDERMOTT: What were the concentrations at thirty-six hours when penicillin was still measurable?

DR. TOMPSETT: The concentrations were remarkably high for penicillin administered with an absorption-delaying agent. Several were from 0.15 to 0.3 unit per cc.

DR. MCDERMOTT: What do you think of the possibility of toxicity?

DR. TOMPSETT: There are possibilities of toxicity. The amount of procaine in 300,000 units of procaine penicillin is 120 mg. The toxicity of a single dose of 120 mg. is not great. That much, I believe, might even be given intravenously within a few minutes without very much danger. It would appear that the only real likelihood of difficulty would arise in those patients who are hypersensitive to procaine. This would not seem to constitute a very serious problem but it should be kept in mind. I wonder what Dr. Gold thinks about the toxicity of procaine?

DR. GOLD: I should think that such doses would be quite safe. There are, of course, individual patients with unusual susceptibility to procaine and every once in a while one hears of a disaster from a small dose which got into the circulation too quickly.

DR. MCDERMOTT: Is this cocaine or procaine?

DR. GOLD: It is true of cocaine but I was speaking of procaine. The safety of procaine as used by the anesthetists lies chiefly in the fact that it is given subcutaneously. They seldom give procaine intramuscularly. In the case of procaine penicillin, of course, one is injecting into the muscle and that results in a situation of a different order from the standpoint of toxicity.

DR. MCDERMOTT: What do you think of the experience with the use of procaine in the treatment of peripheral vascular diseases? It has been given intravenously in doses of 4 mg. per Kg. two or three times a week.

DR. GOLD: It is fairly safe there and I think it is fairly safe in the case of the penicillin preparation. There are those isolated cases of hypersensitivity but I doubt very

much that they ought to influence the use of material like this if it turns out to be an important form of therapy. There is another point I should like to raise. Would not this procaine penicillin do away with the intermittent aspect of treatment? I gained the impression that periods of subeffective concentrations of penicillin in a regimen of treatment may have some advantage.

DR. MCDERMOTT: It might have advantages in some situations but I do not think intermittent therapy has any advantage in the acute infections such as bacterial pneumonia.

DR. GINSBERG: There is another possible complication in the use of procaine penicillin. Do you have any idea how long it takes before the procaine is excreted?

DR. TOMPSETT: No, as yet I do not have that information.

DR. GINSBERG: The point I am trying to make is that procaine is a sulfonamide-inhibitor. In the event that one should give it to a patient to whom one would later need to give sulfonamides, the latter drugs would have no effect until the procaine had disappeared or until it had reached a very low concentration.

DR. MCDERMOTT: The procaine penicillin is absorbed over a period of four or five days. If it is given daily for a long period, that could be a real problem.

DR. GINSBERG: It has been shown in patients given large doses of procaine for local anesthesia that they may absorb enough procaine to cause their blood to develop antisulfonamide activity.

DR. MODELL: How much sulfonamide does 1 mg. of procaine inactivate?

DR. HORSFALL: One mg. of procaine will inactivate about 1 Gm. of sulphonamide.

DR. CATTELL: If the combination is absorbed very slowly, wouldn't the procaine absorption be spread out over a long period of time, just like that of penicillin? Unless the combination has a special toxic property, we can assume that the procaine will be destroyed very quickly. In an animal you can give half a fatal dose every twenty minutes with safety.

DR. MCDERMOTT: That was Dr. Tompsett's point. Even if the total amount used over a period of ten days went into the circulation at one time, it would be less than a fatal dose. I think Dr. Gold's point is very well taken, however, that if a drug can produce a reaction, one must think of the possibility of that reaction in connection with its administration.

VISITOR: Would you comment on the use of penicillin aerosol?

DR. MCDERMOTT: It has limited usefulness. It is an effective way of treating pneumococcal pneumonia but other methods are more convenient. The aerosol maintains effective concentrations of penicillin in the blood but on the whole I believe that for practical purposes the other methods are superior.

INTERNE: I am wondering about the syndrome called "unresolved pneumonia," or the persistence of an x-ray shadow after the patient apparently feels well in every way. Do you believe there is such a thing as unresolved pneumonia?

DR. MCDERMOTT: I suspect there is. It is infrequent but I suspect we will see more of it. The usual case called "unresolved pneumonia" probably never was pneumonia, as you are obviously hinting. It was tuberculosis, or perhaps a carcinoma of the lung. I do believe there is a small group of very elderly patients who would have died of pneumococcus pneumonia prior to the days of antimicrobial therapy and who are being saved or whose illness is being converted into a chronic illness by the new therapy. In some of these patients resolution is incomplete and healing occurs by fibrosis. Have you any ideas on that, Dr. Horsfall?

DR. HORSFALL: I think it will be seen occasionally in younger persons. Already we have seen it in two persons under thirty.

DR. MCDERMOTT: Were they patients who had been extremely ill?

DR. HORSFALL: Very ill indeed and with extensive pneumonia. There was no question about the diagnosis and even subsequent examinations by bronchoscopy

revealed no adequate explanation for the unresolved pneumonia.

DR. MCDERMOTT: Is it your belief that these patients might not have survived prior to the advent of effective antimicrobial therapy?

DR. HORSFALL: Yes. I am inclined to agree with you that it only occurs in the extremely ill.

DR. GOLD: What proportion of the patients with pneumonia who come into the hospital now have primary atypical pneumonia?

DR. MCDERMOTT: In our own service, which is small, it varies. During the winter we may see a great deal of pneumococcal pneumonia and no atypical pneumonia. Then we may have an outbreak of atypical pneumonia. In our service this usually occurs in the late summer and fall. I believe Dr. Horsfall would know whether atypical pneumonia tends to occur in outbreaks, or whether there is a steady month-by-month incidence of it now.

DR. HORSFALL: I think all the evidence suggests that the incidence is relatively constant, far more so than that of bacterial pneumonia. The incidence is somewhat lower in the summer than in the winter.

DR. MCDERMOTT: Is it the most common form of pneumonia?

DR. HORSFALL: At one military installation, where all patients with a fever of 101°F. or more are screened because they must go through the station hospital, there were more than 250 patients in the last year with pneumonia among a total population of about 6,000. Only six of these patients had bacterial pneumonia.

DR. GOLD: The term "virus pneumonia" has not been mentioned in this conference. Practitioners use it freely. How does it apply?

DR. TOMPSETT: The term "primary atypical pneumonia" is used to describe a clinical syndrome which is probably caused by a number of different etiologic agents. Because it is suspected that most of these agents are viruses, the term "virus pneumonia" has come into common usage. It seems preferable, however, to avoid using the term "virus pneumonia" at least until the virus etiology has been established and then a more specific term should be available, as has been the case in psittacosis.

SUMMARY

DR. TOMPSETT: The conference this afternoon has helped to crystallize some of the problems in the treatment of primary pneumonia which have arisen in connection with the development of the highly effective antimicrobial therapy, namely, penicillin, sulfadiazine and streptomycin. After one has made a diagnosis of primary pneumonia, how important is it in these days to establish the causative agent? Is it safe to ignore the causative organism and proceed directly to treat with penicillin? It appears to be the consensus of opinion that detection of the causative organism is still a matter of great importance. If all bacterial pneumonias were due to the pneumococcus, the matter would be very simple because of the ease with which they can be controlled with an antimicrobial agent virtually without toxicity, namely, penicillin, but these constitute only about 95 per cent of the bacterial pneumonias. Most of the others include those due to streptococci, staphylococci, tubercle bacilli and Friedländer's bacilli. Clinically, these cases are often difficult to differentiate, yet it is imperative to do so because their treatment differs. Whereas pneumococcus pneumonia shows dramatic response within twenty-four to forty-eight hours after moderate doses of penicillin, the streptococcus and staphylococcus pneumonias require much larger doses. Special emphasis was laid on the problem of Friedländer's pneumonia. This organism does not respond to penicillin and is best treated by a combination of sulfadiazine and streptomycin. In this disease irreversible changes may be produced within forty-eight hours, so that a delay in appropriate therapy by a mistaken diagnosis may prove disastrous. The satisfactory response to streptomycin of patients with acute tuberculous pneumonia in the exuda-

tive stage adds further weight to the importance of early recognition of the causative agent.

A noteworthy feature of the discussion was the emphasis placed on the so-called primary atypical pneumonias, sometimes referred to as "virus" pneumonias, due to as yet unidentified organisms some of which may be viruses. While the incidence of primary atypical pneumonias is not established, it is clear that they occur very frequently and indications are that their milder forms far exceed those of bacterial pneumonias. These do not respond to any known antimicrobial agents and in them therapy consists essentially of supportive measures applied in relation to symptoms that arise.

The discussion also embraced such items as the need for typing the pneumococcus, the place of the sulfa drugs in the treatment of pneumonias, the causes of failure to respond to therapy, and the various plans for the use of the antimicrobial agents. It was pointed out that when sulfadiazine is necessary, 2 Gm. may serve as the initial dose followed by 1 Gm. every four hours. In the case of streptomycin, the usual dose is from 20 to 40 mg. per Kg. daily or about 1 to 2 Gm. a day for the average adult by intramuscular injection in three or four fractions. Interesting experience was related showing that current schedules of intramuscular injection of penicillin at intervals of three to four hours in the treatment of pneumococcal pneumonia may no longer be necessary and equally satisfactory results may be obtained by the intramuscular injection of 300,000 units dissolved in 1 cc. of saline and given at intervals of twelve to twenty-four hours. The discussion also touched on a new procaine-penicillin compound which, by virtue of the fact that it is insoluble, may produce unusually sustained high blood levels after a single dose. This is still in the experimental stage.

Clinico-pathologic Conference

Pulmonary Disease of Unknown Origin*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinicopathologic conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient F. B., (B. H. History No. 138724), a forty-five year old white married housewife, entered the Barnes Hospital for the first time on August 22, 1946, complaining of cough of approximately two years' duration. The family history was non-contributory. The past history was of interest in that the patient had had typhoid fever as a child. She stated that she had never enjoyed good health nor had she been robust and her appetite had been poor for a number of years. Prior to marriage she worked in a newspaper office and had been extremely fatigued at night. However, she had been free of symptoms of any definite illness until 1942, at which time she developed complaints referable to the gastrointestinal tract. X-ray studies were said to have revealed a pathologic gallbladder and at the same time she was told that she had a "positive test for brucellosis"; the nature of the diagnostic procedure was not known. At that time "vaccine therapy" was begun and it was continued for four years, being discontinued only two months prior to her admission to this hospital. At no time had she had symptoms which suggested brucellosis. In March of 1945, because of irregular and prolonged menstrual periods, the patient underwent dilatation and curettage of the uterus. Extreme hyperplasia of the endometrium was said to have been found and total hysterectomy was subsequently performed. Subsequently she was given monthly injections of "20,000 units of an estrogenic substance." Postoperatively, she developed an upper respiratory infection and cough and lost about 15 pounds in the ensuing six months. In January, 1946, flatulence again appeared and gastrointestinal roentgenograms were made. They were said to have shown "a dilated 2nd and 3rd portion of the duodenum"; concomitantly, the patient noted stiffness, swelling and some redness about the phalangeal joints which persisted for a few months and then subsided spontaneously. She was seen in a diagnostic clinic in Chicago where a number of studies were performed and among them a normal chest film was recorded. Her abdominal complaints, particularly fullness and tightness of the upper abdomen immediately after eating, persisted and she had occasional nausea and vomiting for ten to thirty minutes after meals which relieved her symptoms. She restricted her diet to 1 quart of milk a day, lettuce, carrots and graham crackers. Her weight fell to 90 pounds. Further x-ray studies were made and the patient was told that she had "a sinus infection" but that her chest films continued to be negative. On examination her abdomen was described as showing a "doughy resistance" but no other abnormalities were detected.

Laboratory studies, according to reports received from the clinic in Chicago, indicated that the patient's red blood count was normal. Her urine contained a trace of albumin and the blood non-protein nitrogen, cholesterol, calcium and phosphorus were all said to have been within

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.

normal limits. The basal metabolism rate was −8. She was admitted to a hospital where a laparotomy was performed to "elucidate the roentgenographic findings." The operative note stated that the only abnormalities consisted of a small, shrunken, knobby spleen and dilatation of the 2nd and 3rd portions of the duodenum. The gallbladder was said to have appeared normal and the site of the previous operation was well healed. No adhesions were present. The kidneys were normal to palpation. A mesenteric lymph node was removed and on subsequent microscopic study was reported as showing only chronic inflammation. Duodenojejunostomy was performed. At the time of her discharge from the outside hospital the patient weighed only 84 pounds.

As stated, the patient had had an upper respiratory infection with cough following her hysterectomy two and one-half years previously. Subsequently, cough had occurred in association with a postnasal discharge in the morning. Shortly after her second abdominal operation and one month prior to her admission to the Barnes Hospital, the patient again began to note a persistent cough which was described as severe, was present both day and night and was productive of purulent sputum; at no time was the sputum bloody. The patient also stated that she had had some dyspnea on exertion and slight swelling of the feet and ankles at night. Although she occasionally had pain in the left chest, at no time did she note chills or night sweats and her maximum temperature had been 100°F.

Physical examination on entry revealed the patient's temperature to be 38.5°c., pulse 120, respirations 44 and blood pressure 120/60. She was an emaciated, rather dehydrated female who looked much older than her stated age. She coughed frequently and complained of pain throughout the left chest and upper abdomen. Chest excursion appeared limited because of pain. The skin was warm and no eruption was seen. Examination of the eyes revealed that the pupils reacted well and the optic fundi were normal. The left ear drum was dull and somewhat retracted. Mucopurulent secretions were present in the nares and the pharynx appeared granular; lymphoid hyperplasia was seen. A mucopurulent discharge likewise covered the posterior pharynx. The tonsils were slightly enlarged. There was kyphoscoliosis of the spine and chest was therefore asymmetric. Retraction of the left ninth, tenth and eleventh interspaces on inspiration was described and over the left chest posteriorly resonance was impaired and tactile fremitus, breath sounds and voice sounds were diminished. A few moist râles were heard throughout both lungs. Except for the rapid rate the heart appeared normal to examination. Two abdominal scars appeared well healed. On examination of the abdomen there was tenderness in the right upper quadrant but no organs or masses were felt. The fingers were not clubbed and there was no edema. The remainder of the physical examination was negative.

The laboratory studies were as follows: Blood count: red cells, 3,830,000; hemoglobin, 10.2 Gm.; white cells, 22,200; differential count: stab forms, 13 per cent; segmented forms, 68 per cent; lymphocytes, 16 per cent; monocytes, 3 per cent. Urinalysis: albumin, trace; sediment, many white blood cells. Stool: guaiac negative. Blood Kahn test: negative. Sputum examination: no acid-fast bacilli seen. Blood chemistry: fasting sugar, 63 mg. per cent; non-protein nitrogen, 13 mg. per cent; total protein, 5.8 Gm. per cent; albumin, 3.0 Gm. per cent; globulin, 2.8 Gm. per cent. Electrocardiogram: normal. Roentgenogram of the chest (Fig. 1): "The cardiac silhouette and the aorta are within normal limits. There is a dense infiltration in the perihilar region on the left side extending out to the lateral zone of the lung; its margins are very well demarcated and it appears lobulated. In the oblique view the abnormal findings are located in the left lower lobe. There is generalized haziness over the entire lower left chest, suggesting the presence of a small amount of fluid.

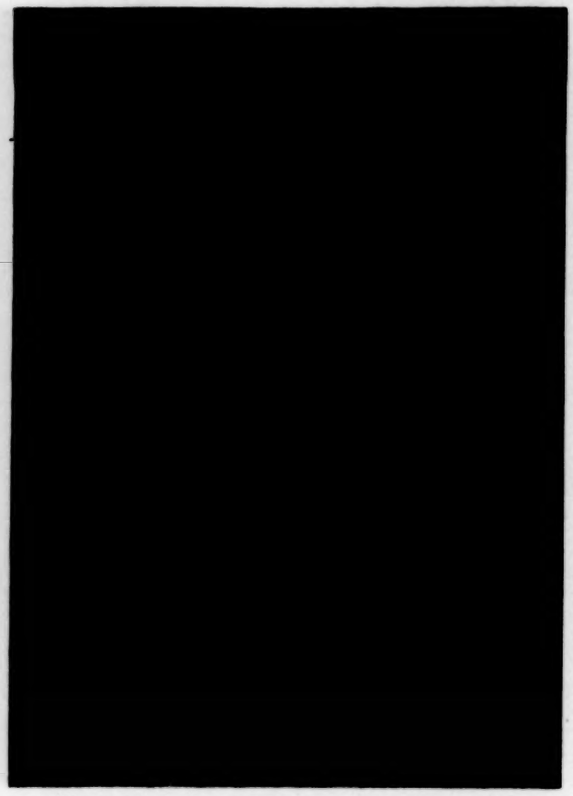


FIG. 1. Roentgenogram of the chest taken during the first admission. There is bilateral pulmonary infiltration and fluid is present in the left pleural cavity.

On the right side there is a dense infiltration in the inferior portion of the hilus but the margins are not well demarcated; lung markings are slightly coarse along the descending bronchi in this area. The exact nature of these masses is not known but it is thought that they represent a tumor in both perihilar regions with fluid in the left pleural cavity."

During her stay in the hospital the patient coughed almost incessantly and continued to produce mucopurulent sputum which on repeated examinations contained no acid-fast bacilli. On culture, coliform organisms were reported. The patient was transferred to the Chest Surgical Service and a thoracentesis was done. Three-hundred cc. of amber bloody fluid were obtained which clotted promptly. On culture, no organisms were noted and cultures for fungi on Sabouraud's medium were likewise negative. Some of the material was inoculated into a guinea pig but the animal remained well. Cell blocks were made on the sediment and no tumor cells were seen in the sections of these.

A bronchoscopy was performed and no abnormalities were found other than inflammation of the bronchial mucosa. The mucosa was biopsied and was reported as showing only chronic inflammation. The patient's temperature ranged between 38 and 39°C. and did not respond favorably to penicillin therapy. Agglutination tests for brucellosis were reported positive in a dilution of 1:320. Because no definitive diagnosis could be made, the patient was exposed to treatment with roentgen rays. About three weeks later she began to improve; the cough lessened, the fever subsided and the chest signs cleared although signs of consolidation or fluid at the left base persisted and some râles were still audible. Subsequently, there appeared to be an increase in fluid in the left pleural cavity but no other changes in the pulmonary findings. The patient was transferred back to the Medical Service and on examination at that time her liver was palpable 8 cm. below the right costal margin and there was bilateral ankle edema. The patient complained of moderate diarrhea. She was given a high protein diet, large amounts of vitamins and two blood transfusions. Further laboratory studies were as follows: Blood count: red cells, 4,250,000; white cells, 13,350. Total protein: 5.1 Gm. per cent; albumin, 2.4 Gm. per cent; globulin, 2.7 Gm. per cent. Icterus index: 6; cephalin-cholesterol flocculation, 3+. Examinations of the sputum and of the gastric washings were continued but at no time were tubercle bacilli found. Just prior to discharge the patient was again examined on the Chest Service and clearing of the infiltrative lesions was described; the fluid in the left pleural cavity persisted. The liver had decreased in size and the edema had diminished. When the patient left the hospital on September 6, 1946, she appeared to be in better health and stated that she felt much improved. She returned to her home and the care of her private

physician. During the first two months she remained at home her appetite improved and she gained weight. The cough bothered her much less and she seemed to be getting on quite well until three weeks before her second and last admission at which time the cough again increased and hoarseness appeared. Her temperature, which had been normal, rose to 101°F. and anorexia and great fatigue were again noted; on December 14, 1946, the patient was readmitted to the Barnes Hospital.

All the time of entry her temperature was 38°C., pulse 110, respirations 30 and blood pressure 110/70. She appeared extremely emaciated and very ill. She was orthopneic and dyspneic and could speak only in a harsh whisper. Respirations were punctuated by frequent paroxysms of cough productive of thick yellowish-green sputum. The nares contained purulent secretions. Expansion of the left chest was limited and there was dullness over the lower half of both lungs posteriorly. Over the areas of dullness breath sounds and voice sounds were diminished and the breath sounds were bronchovesicular in character. Moist râles were heard bilaterally above the areas of dullness. The heart seemed normal to examination. The liver edge was questionably felt 5 cm. below the costal margin and clubbing of the fingers had appeared. Laboratory data included the following: Blood count: red cells, 4,680,000; hemoglobin, 14.4 Gm.; white cells, 15,000; differential count: eosinophiles, 1 per cent; stab forms, 11 per cent; segmented forms, 69 per cent; lymphocytes, 12 per cent; monocytes, 7 per cent. Urinalysis: negative. Venous pressure: 150 mm. of water. Circulation time (decholin): 15 seconds. Vital capacity: 450 cc. Sputum examination: negative for acid-fast organisms. Blood chemistry: non-protein nitrogen, 21 mg. per cent; total protein, 5.8 Gm. per cent; albumin, 2.6 Gm. per cent; globulin, 3.2 Gm. per cent. Roentgenogram of the chest (Fig. 2): "There is no evidence of fluid in the left pleural cavity. Fibrosis extends outward from both hilar regions and is greater in extent than was previously noted but its density does not appear increased."

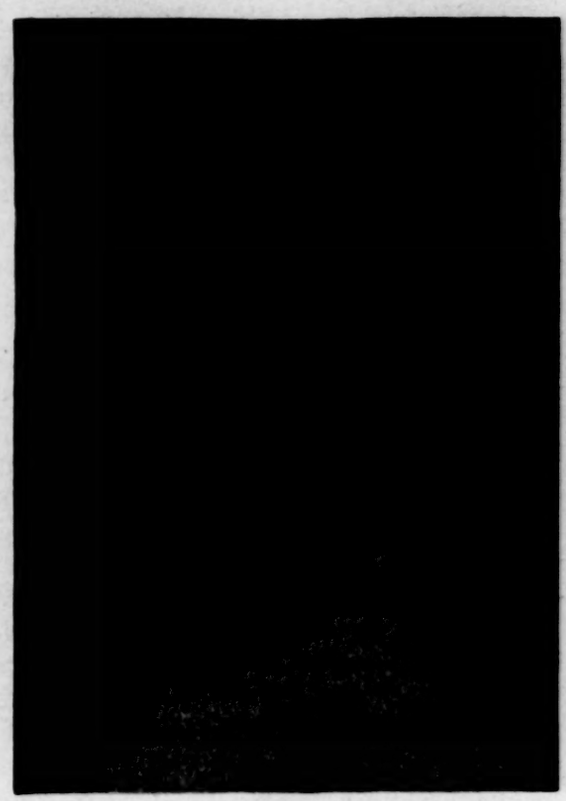


FIG. 2. Another roentgenogram of the chest made during the second admission. There has been an increase in the amount of fibrosis but the pleural effusion is no longer present.

The patient was seen in consultation by an otolaryngologist. On laryngoscopic examination of the larynx he found the mucous membrane to be dull red in color; there was thick yellow pus on the posterior wall of the hypopharynx. The arytenoids moved normally. There was crusting involving the anterior third of the larynx and considerable crusting below the cords but no evidence of tumor was noted. It was thought that the hoarseness was a result of the pulmonary infection with drying of the secretions around the larynx. The patient remained critically ill; her temperature ranged between 38 and 39°C. and her pulse averaged 130. Weakness was extreme and symptomatic treatment brought no improvement. Two days after admission she was found sitting upright in bed, confused and unresponsive. The signs in the lungs

had not changed from those recorded on admission. Cyanosis was present and pitting edema of the ankles had reappeared. The white blood cell count had risen to 26,500. In spite of the administration of oxygen and penicillin the patient failed to improve and she died on December 27, 1946.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This patient was in the Barnes Hospital on two occasions and each time was exposed to all the diagnostic facilities available; yet on neither occasion could a diagnosis be established and the problem still remains for us today to attempt to establish the nature of the pulmonary lesion. Likewise, the question of whether the patient had other visceral lesions must be considered, particularly in view of the fact that at the time of her second laparotomy the spleen was described as small and knobby. It seems probable that the patient had hepatic involvement and it is conceivable that all of her lesions were related. In reviewing the history it is interesting to note that approximately two years before her final illness she developed some respiratory symptoms, particularly cough, following a hysterectomy. We are told, however, that at the time of onset of the symptoms she was seen in a clinic in Chicago and had a negative chest film; furthermore, a negative chest film was reported as recently as one and one-half months prior to entry here. If that information is correct, we are probably dealing with a fairly acute process and we must prove that the lesions which were found in a chest film taken on admission to this hospital had not been present some months before. Dr. Goldman, the radiologists interpreted the first chest film as indicating the presence of a tumor; in view of the course and the other information available do you agree with that diagnosis?

DR. ALFRED GOLDMAN: I think that at that time I would have made the same suggestion. The hilar lesions were bilateral and certainly suggested malignancy.

DR. ALEXANDER: Do you believe that the patient could have developed a lymphoma or metastases from a bronchogenic carcinoma in one month?

DR. GOLDMAN: No, I think that period of time is probably much too short.

DR. ALEXANDER: What is your opinion, Dr. Moore, in regard to the development of a mediastinal lymphoma in a period of one month?

DR. CARL V. MOORE: I do not believe this patient had a lymphoma but lymphomatous enlargement of the mediastinum may appear very rapidly, even within one month. My reasons for discarding that diagnosis in this particular instance lay in the absence of other signs. If the patient had had Hodgkin's disease or lymphosarcoma, one would have expected that at some time during the course of her illness she would have developed enlargement of some other lymph nodes. There was neither lymphopenia nor monocytosis and although the absence of these does not rule out Hodgkin's disease, it makes it quite unlikely. Further, splenomegaly and severe anemia would be expected had this been a lymphomatous disease. I believe all of the considerations enumerated mitigate strongly against that possibility.

DR. ALEXANDER: If the patient had a lymphoma, could the apparent respiratory infection be related to it?

DR. C. V. MOORE: No, I believe the infection would have to be considered as a separate, unrelated entity.

DR. ALEXANDER: From the data at hand, we are led to believe that the infection involved the sinuses, the larynx and the bronchi. Dr. Harford, have you any suggestions as to the etiology of this rather widespread process?

DR. CARL G. HARFORD: I was impressed by the fact that the patient's cough originally appeared shortly after an abdominal operation and also by the fact that on both examinations here purulent secretions were described in the upper respiratory tract. It seems conceivable to me that during the course of the operation exudate in the upper

respiratory tract was aspirated into the lungs and gave rise to one or more lung abscesses.

DR. ALEXANDER: Your point is very well taken. Aspiration pneumonia must certainly be considered. In view of the fact that coliform bacilli were cultured in the sputum, I should like to ask whether colon bacilli are commonly found in gastric secretions.

DR. HARFORD: They may occur there occasionally.

DR. ALEXANDER: Dr. Wood, do you think that there is any direct connection between the abdominal operation and the finding of colon bacilli in the sputum?

DR. W. BARRY WOOD, JR.: No, I do not think so. I am impressed, as Dr. Goldman is, by the response of the pulmonary lesion to x-ray therapy. It seems to me that this observation rules out most of the common infections.

DR. ALEXANDER: Tuberculosis must be considered but attempts to substantiate that diagnosis by the finding of tubercle bacilli in the sputum were pursued diligently and no acid-fast bacilli were ever found. If this had been tuberculous pneumonia, Dr. Goldman, do you think that tubercle bacilli would have been found?

DR. GOLDMAN: I would certainly think so.

DR. ALEXANDER: When Dr. Thomas Burford bronchoscoped the patient, he noted the inflammatory changes described in the protocol. X-ray therapy was given in the hope that liquefaction of the area of induration in the lung might be achieved, thus making it possible for the patient to cough up the necrotic material more easily.

DR. DONALD S. BOTTOM: The patient received more exposure to radiant energy than one would advise for the treatment of an infection. The total dosage given was designed to effect a radiosensitive tumor, a therapeutic trial as it were.

DR. ALEXANDER: I should state that there was some controversy in the Chest Service as to the diagnosis. Some members believed that the patient had a tumor, perhaps one of the lymphomas. Boeck's sarcoid was also mentioned.

DR. BOTTOM: The clinical diagnosis which we received was, "questionable tumor of both lungs of unknown origin," and it was on the basis of this diagnosis that the patient received the amount of radiation given.

DR. ALEXANDER: Would the amount of x-ray administered have aided in breaking down an indurated lung?

DR. BOTTOM: It probably would have led to more destruction than would have been desirable. The amount of radiant energy given would have reduced a very sensitive tumor in size; but had the patient had inflammatory induration of the lung, abscess formation probably would have occurred.

DR. ALEXANDER: It might be well for me to summarize the opinion of the members of the Chest Surgical Service. The record stated, "It was felt by some that the most likely diagnosis was a malignant lymphoma of the mediastinum. Dr. Evarts Graham felt that a bilateral inflammatory process was more likely." Here, aspiration pneumonia has been suggested and no conclusive support for malignancy has been forthcoming.

DR. BERTRARD Y. GLASSBERG: I believe this patient may have had a systemic infection which was quiescent until a few months before her death. One remote possibility worthy of mention is histoplasmosis. I am unaware of the sensitivity of pulmonary histoplasmosis to radiant energy.

DR. BOTTOM: As far as I know, pulmonary infection due to Histoplasma capsulatum is not favorably influenced by x-ray therapy.

DR. ALEXANDER: Was not the white blood cell count rather high for histoplasmosis?

DR. WOOD: Yes. In typical cases white cell counts of a much lower order are seen.

DR. ALEXANDER: Although the patient received "vaccine treatment" for brucellosis, at no time did she have symptoms suggestive of that disease and it seems to me unlikely that the pulmonary findings could be explained on that basis.

DR. MARGARET L. J. HENRY: Is it possible that the repeated injections of brucella vaccine produced a state of hypersensitivity and a generalized vascular disease?

DR. ALEXANDER: That is a very interesting suggestion since we know that the patient did receive vaccine therapy for years; however, since the exact nature of the vaccine is not known we cannot comment on its antigenicity. I think the possibility of fungus infection in the lung must be mentioned in passing although repeated specimens of sputum were cultured on Sabouraud's medium and no organisms were recovered.

DR. GOLDMAN: One must consider actinomycosis, blastomycosis or torulosis but in most of these skin lesions are seen and the negative results on bacteriologic study tend to rule them out.

DR. ALEXANDER: Dr. Wade, would you comment on the possibility of liver disease?

DR. LEO J. WADE: The laboratory data suggest liver involvement as evidenced by a 3+ cephalin-cholesterol flocculation test and the reversal of the albumin-globulin ratio. Of course, if the pulmonary infection were due to a chronic granuloma, one might well find elevation of the serum globulin. However, if there were no chronic granuloma in the lung, the reversed albumin-globulin ratio would point to primary liver disease. Furthermore, the anemia is consistent with hepatic involvement. I do not believe, however, that the patient had cirrhosis.

DR. ALEXANDER: What type of granulomatous lesion did you have in mind?

DR. WADE: I was referring to the chronic infections already mentioned.

DR. GOLDMAN: Two other diagnostic possibilities should be mentioned in passing. First, there is no history of repeated use of oil-base nose drops but lipoid pneumonia is one of the causes of chronic pulmonary inflammation such as may be present here. It seems entirely conceivable that this patient, who had a chronic upper respiratory infection, may have used some such oily preparation. Likewise, pulmonary adenomatosis may give a radiologic picture such as seen here and, although rare, may be considered.

DR. ALEXANDER: Are the lesions of pulmonary adenomatosis radiosensitive?

DR. BOTTOM: There have been so very few cases reported that I am unable to answer your question.

DR. ALEXANDER: I think both of Dr. Goldman's suggestions are excellent; either one of them could have given rise to the course observed in this case.

DR. WOOD: Dr. Alexander, have you completely discarded Boeck's sarcoid as a diagnostic possibility?

DR. ALEXANDER: Yes, I have. Do you think it merits further consideration, Dr. Wood?

DR. WOOD: Yes, I do, for I do not see how it can be ruled out on the basis of the data available.

DR. GOLDMAN: The response to x-ray which this patient exhibited is compatible with sarcoid and the bilateral hilar enlargement likewise is consistent.

DR. ALEXANDER: The course seems too rapid for sarcoid in my experience.

DR. WADE: Although the patient eventually developed a reversal of the albumin-globulin ratio, at no time was the serum globulin elevated *per se*.

DR. ALEXANDER: I am not sure that hyperglobulinemia is a universal finding in sarcoid although it is certainly very common.

DR. WADE: I agree Dr. Alexander with your statement, but I would expect the globulin value to be at the upper limit of normal in any case.

DR. ALEXANDER: In summary, then, one may say that a number of diagnoses have been suggested to explain this very complex clinical picture; included have been malignant lymphoma, chronic infections such as tuberculosis and fungus disease, sarcoid, lipoid pneumonia and pulmonary adenomatosis. I am afraid we will have to rely on the pathologists to clarify the situation, however, for we have been unable to rule in or out definitely any of the possibilities.

Clinical Diagnoses: ?Malignant lymphoma of the mediastinum; ?chronic pulmonary infection; ?sarcoid, lipoid pneumonia or pulmonary adenomatosis.

PATHOLOGIC DISCUSSION

DR. BETTY B. GEREN: At autopsy the body was that of a well developed but very poorly nourished white woman who weighed 42 Kg. There were circular areas of depigmentation about the mammary areoli. The heart weighed 270 Gm. and there was slight sclerosis of the coronary arteries. The liver weighed 1,550 Gm. and was soft in consistency; there were yellowish white markings in the periphery of the lobules as seen on section. The gastrointestinal tract was essentially normal except for small erosions of the gastric mucosa. The kidneys were slightly granular and weighed 190 Gm. each. The spleen was very small, weighing only 35 Gm.; there were two whitish pyramidal foci at its periphery measuring 0.5 cm. in diameter. The uterus, ovaries and fallopian tubes were absent.

The lungs weighed 1,130 Gm.; over the pleural surfaces there were a large number of clear and fibrous adhesions. The right pleural space contained 100 cc. of serosanguineous fluid and the left pleural space contained about 500 cc. of similar fluid. The tracheobronchial tree contained a moderately large amount of thick, yellowish, purulent material. On section of the lungs there were three types of nodular lesions. Scattered through all the lobes of both lungs were firm, yellowish, granular, slightly elevated nodules varying from 0.5 to 1.5 cm. in diameter, some of which showed small, white, firm foci at their centers. The second type of nodule was extremely firm, pale yellow-white in color, sharply circumscribed and slightly bulging; these varied from 1 to 2 cm. in diameter and were found in the lower lobes of both lungs. In the left lower lobe these nodules formed a large mass which involved the pleura and the adjacent soft tissues of the chest wall and measured 8 by 5 by 2 cm. The third type of nodule was found in the lobes of the left lung; in the upper lobe there was a 2.5 by 1 by 1 cm. irregularly shaped focus that was firm and bright yellow. The pulmonary parenchyma around the focus showed atelectasis with an increased amount of edematous interstitial fibrous tissue. In the left lower lobe there was a 1 by 1 by 1 cm. bright yellow, moderately firm lesion which was flat when cut; it was surrounded by pulmonary tissue which likewise was partially replaced by edematous fibrous tissue. On the posterior surface of the right lower lobe there was a 4 by 4 by 0.3 cm. opaque, slightly retracted focus of pleural thickening. The pulmonary parenchyma underlying this focus showed changes similar to those seen throughout the right lower lobe, that is, considerable increase in fibrous tissue.

DR. ROBERT A. MOORE: I think that this case will be particularly enlightening if I present it to you much as it was unfolded to us as we studied it. You will remember that on the basis of the gross examination the two organs that showed major pathologic changes were the lungs and the spleen. The spleen was small and firm and from the gross examination one could make no other diagnosis than "atrophy of the spleen." In the lung there was a disease process producing irregular nodules of varying size, yellow and grey in color, associated with fibrosis in some areas and with only a small amount of fibrous proliferation in other areas. Thus, our gross diagnosis at the time of autopsy was that of a chronic granulomatous disease involving the lungs and possibly the spleen. Figure 3 is a section of the lung, showing a bronchus. There is metaplasia of the epithelium and destruction of the wall. The lumen extends almost to the muscle which indicates that most of the tissue in between has been destroyed. In the lumen there is an exudate consisting of fibrin and polymorphonuclear leukocytes and in some places the exudate is undergoing necrosis. Larger cells are seen, macrophages, which are filled with numerous vacuoles which probably contain fat. In Figure 4, in another area of the lung, the typical picture of acute bronchopneumonia

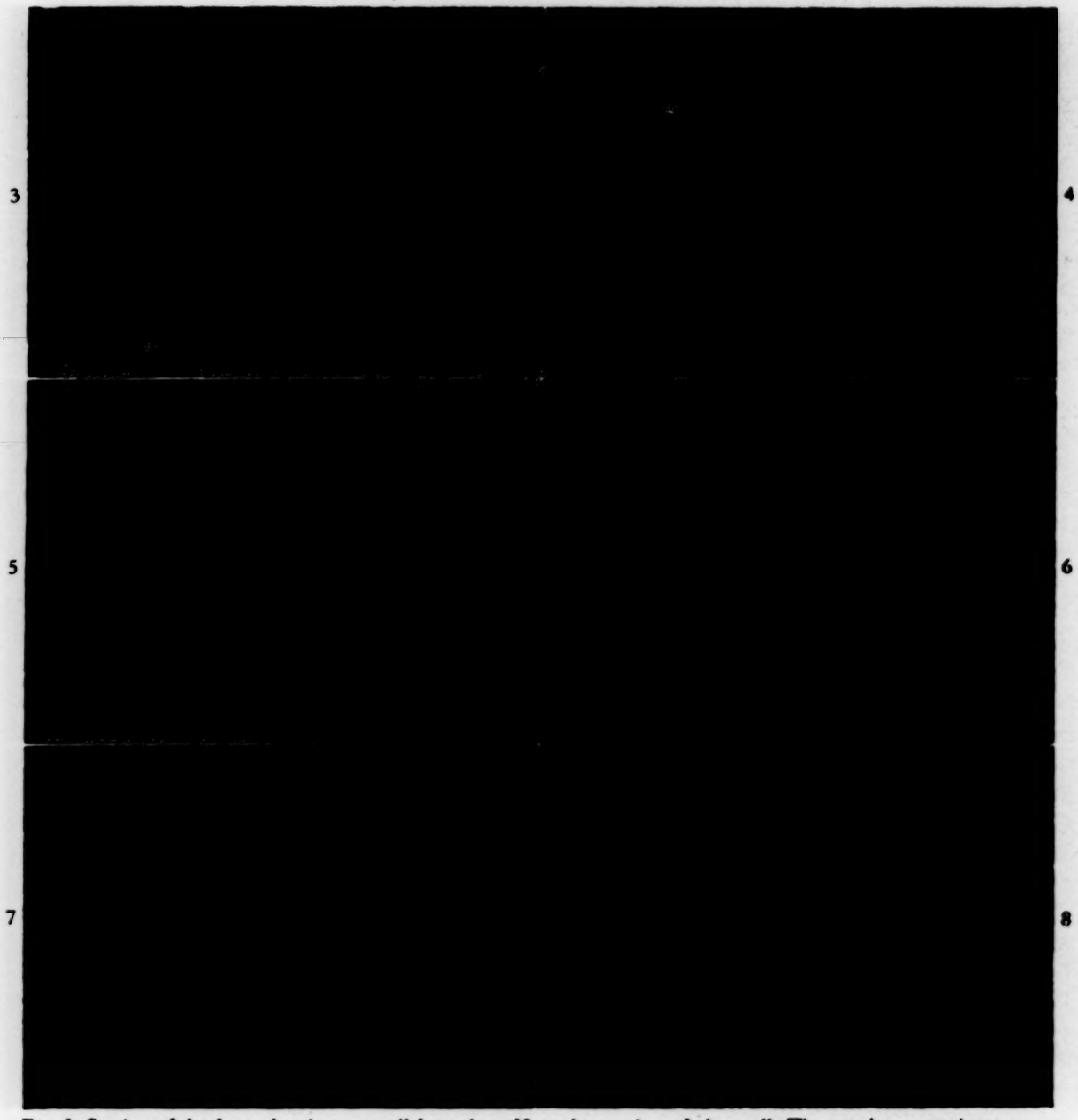


FIG. 3. Section of the lung showing a small bronchus. Note destruction of the wall. The exudate contains macrophages which are filled with vacuoles, probably fat.
FIG. 4. Another section of the lung showing an area of acute bronchopneumonia. Here the exudate contains chiefly polymorphonuclear leukocytes.
FIG. 5. Higher power view of the lung showing the macrophages distended with fat globules.
FIG. 6. Section through an area of organizing pneumonia.
FIG. 7. Another area of the lung which has undergone fibrotic changes. Note that the tissue spaces are lined with cuboidal epithelium.
FIG. 8. Still another section through the lung showing an area where necrosis has occurred.

may be seen. The alveolar walls are not thickened and the alveolar spaces contain only a small amount of fibrin. Numerous polymorphonuclear leukocytes are present. In another section of the lung (Fig. 5), the alveoli are filled with large macrophages which are tremendously distended with fat globules; special fat stains showed that each of the small vacuoles seen in the macrophages represented a tiny droplet of fat and, indeed, this finding constituted one of the most prominent features of the microscopic examination of the lung. It should be noted that cuboidal cells line the surface of the alveolar wall, an indication of chronic disease in the lung. In Figure 6 another region of the lung is shown and the pathologic picture is typical of that seen in organizing pneumonia. The alveolar spaces have been replaced in part by fibrillary tissue and some of the fat-laden macrophages are isolated within the fibrous tissue. In the periphery of this section the process represents the changes of an acute pneumonia such as was seen in Figure 2. Figure 7 shows an area of fibrosis in the lung. In the gross examination it appeared as grey, dense, moderately mature connective tissue. Here the spaces are lined with cuboidal epithelium. In Figure 8, a mass of pulmonary tissue undergoing necrosis is seen. The nuclei have disappeared in the necrotic area and the boundary between the living and necrotic tissue is relatively sharp.

Sections of the spleen showed extreme atrophy and fibrosis. The Malpighian bodies were practically absent and in a few areas foci of necrosis were seen. The liver showed a small amount of fatty infiltration and central necrosis of recent origin but no other lesion which could be related to the major process. Microscopic examination of the other organs revealed no significant abnormalities.

Our problem, of course, was to attempt to determine the nature of the disease which led to this patient's death. One of the first considerations is to remember the organs involved. They include the lungs, liver and spleen. The atrophy of the spleen does not seem to me to be specific and for that reason I am of the opinion that the changes have no bearing on the principal disease from which the patient suffered. The changes in the liver were likewise not of sufficient magnitude to be considered part of the major disease. The central necrosis probably resulted from anoxia during the terminal stage of the patient's life. The lymph nodes contained no specific lesions related to those found in the lungs and can be discarded as having no bearing on the major disease. We thus come to the point where it appears that the major disease process in this patient involved only the lungs.

Let us summarize again the character of the pulmonary disease. First, there was exudative inflammation of the acute variety with polymorphonuclear leukocytes and fibrin. Second, bland foci of necrosis up to 7 mm. in diameter were seen. Third, a prominent part of the picture was the presence of many macrophages containing a large number of finely divided fat particles. Fourth, there was an organizing pneumonia and fifth and finally, areas of fibrosis were common. I believe it is helpful to list these five features, for in arriving at the etiology of the changes it is necessary to find an agent that is capable of producing changes covering the entire range of inflammation, that is, from acute inflammation to fibrosis. Of the diagnostic suggestions made in the clinical discussion, certainly neoplasm may be ruled out immediately for there is no evidence of any malignant process. As to infectious agents which may have produced this disease it was pointed out that conceivably the tubercle bacillus could have been responsible. Brucellosis can likewise produce lesions of the type seen here but does not characteristically do so in the lung without involving the liver and spleen as well. Much information can be gotten from cultures and staining of the tissue for various bacteria. Aerobic and anaerobic cultures from the lung revealed only staphylococci and Vincent's organisms. Culture of splenic tissues, carried out under increased carbon dioxide tension in an

attempt to recover brucella organisms, was negative. Sections of the lungs stained from bacteria again showed only gram-positive cocci and the Vincent's fusiform organisms and the staphylococci which are present are not intimately associated with the lesions which you have seen. Dr. Parker Beamer searched suitably stained sections for tubercle bacilli for hours and was unable to find any. Likewise, no fungi could be demonstrated and none were recovered on culture on Sabouraud's medium.

We next turn to a consideration of physical agents which might have been responsible for the changes seen here. Radiant energy may be ruled out by the fact that the lesion was obviously present before the radiation therapy had been given and the changes are not typically those seen within three months of the date of exposure to roentgen rays. Let us then turn to the problem of the fat-containing macrophages. The amount of fat present is greatly out of proportion to the amount which would be expected in simple organizing pneumonia or a destructive process in the lungs *per se*. It is true that fat accumulates in any inflammatory process in which tissue has been destroyed, but there is not sufficient destruction here to explain the great number of fat-containing macrophages. We therefore come to the possibility that the patient had lipoid pneumonia as suggested by Dr. Goldman. The pathologic changes are entirely consistent with that diagnosis if one makes the assumption that the lipoid which was introduced into the lung was a saponifiable fat from which fatty acids could have been liberated. It is not characteristically the type of lipoid pneumonia seen with a non-saponifiable fat such as mineral oil for the latter accumulates in large droplets, there is more fibrosis and fatty macrophages are not seen. However, if the fat is saponifiable, this represents a typical clinical picture. I can think of no other possible explanation. In an attempt to substantiate the diagnosis we contacted various physicians in other cities who had taken care of this patient. Several stated, "Yes, this patient had used a large amount of some type of nose drops but I do not know their nature because they were purchased by her at a drugstore without a prescription."

DR. ALEXANDER: Is there any possibility that this woman had fat embolism at the time of injection of the estrogenic substances?

DR. R. A. MOORE: I think the amount of fat present is much too great for that.

DR. ALEXANDER: I would like to ask Dr. Goldman if one may find fat in the sputum by proper staining.

DR. GOLDMAN: I believe there are several cases on record in which that was done.

DR. R. A. MOORE: This diagnosis could possibly have been made clinically if the sputum had been stained for fat.

Final Anatomic Diagnoses: Lipoid pneumonia of all lobes of the lungs with organization and necrosis (presumably caused by a saponifiable fat); fibrous pleural adhesions, bilateral; pleural effusion, serosanguineous fluid (right 100 cc.; left 500 cc.); atrophy of the spleen; central necrosis of liver; acute erosions of the gastric mucosa.

Bcateriology: Lung, aerobic: (pure culture) hemolytic *Staph. Aureus*. Spleen, no growth aerobically, anaerobically or under increased CO_2 tension.

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Case Report

Complete Heart Block in a Case of Pregnancy*

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THE historical record of the disorder we now recognize as complete heart block is of interest in that Morgagni recorded the first case of heart block in the year 1761, but it was nearly a century later before clinical accounts of this disorder were published by Robert Adams and William Stokes.[1] In 1893, His contributed immeasurably to the understanding of heart block and in 1903 Von Stark[2] called attention to the fact that complete heart block could occur on the basis of a congenital defect in the conduction system.

In the early part of the present century clinicians became more interested in recognizing and reporting cases of congenital complete heart block, and in 1920 Carter and Howland[3] reviewed seven established cases and added one of their own. Yater[2] in 1929 reported a case of an infant whose heart beat two weeks before birth was found to be slower than the mother's heart rate. This child died soon after birth and at autopsy several congenital anomalies were found including complete situs inversus. On dissection the A.V. node was found to be completely separated from the A.V. bundle.

Yater et al.,[4] in 1933, reported another case of an infant with complete congenital heart block. The autopsy on this patient revealed a defect in the interventricular septum and almost complete absence of the bundle of His. These authors deemed it necessary to proclaim certain criteria for the proper diagnosis of congenital complete heart block and their standards were: (1) bradycardia which must have been noted at an early age; (2) no history of infection such as diphtheria, rheumatic fever, chorea or congenital lues which might have caused the heart block, and finally (3) proof by graphic means. The additional signs which add weight to the diagnosis of this disorder are the occurrence of syncopal attacks at an early age and evidence of definite features of congenital heart disease. The authors also assert that the causes of congenital complete heart block are: (1) developmental defect of the bundle of His; (2) prenatal endomyocarditis and (3) congenital lues with involvement of the bundle of His.

In 1934, Yater, Leaman and Cornell[5] reported the third case of congenital complete heart block studied by serial section through the conduction system. This patient was an infant who was cyanotic at birth and was found to have a complete heart block with a rate of 40 as confirmed by electrocardiogram. The patient expired after eighteen hours and autopsy disclosed an interauricular septal defect, a marked defect of the interventricular septum and a lack of continuity between the bundle of His and the A.V. node.

Campbell and Suzman[6] reported on eight cases and emphasized that the disorder

* From the Department of Medicine, School of Medicine of the Southwestern Medical Foundation. Read before the Texas State Heart Association, May 6, 1945.

of complete congenital heart block is more common than previously considered. The ventricular rate in their patients ranged from 42 to 56 and quickened to 60 or faster on exercise. The authors observed an Adam-Stokes seizure in one of their eight patients. They emphasized that frequently there was some degree of patency of the interventricular septum and usually a prominence of the pulmonary conus. It was the opinion of these authors that the prognosis in such cases was usually good if the associated malformation was not serious. They concluded that the congenital malformation and not the complete heart block is the determining factor in the prognosis and they reiterate that heart block itself may be compatible with a perfectly normal life.

Wenner[7] in 1944 called attention to the eighty-five authentic cases of congenital complete heart block that have been reported and added another. This author pointed out that clinical signs of congenital heart disease and syncopal attacks in young children are valuable evidence of the congenital nature of the block. He also observed that an interventricular septal defect is the most common lesion noted. Wallgren and Windblad[8] found signs of this defect in fifty-one of the seventy-seven cases they reviewed, and in addition, a large number of these patients had other associated anomalies such as pulmonary artery stenosis, patent ductus arteriosus and dextrocardia. In six of eleven patients examined at autopsy definite information concerning the conduction system was found. A break in the system was noted most often just below the A.V. node and in four patients there was severing of the bundle of His by fibrous tissue; "a developmental disunity in the tissues of the conduction system."

There are a number of interesting and useful clinical facts to be derived from the accounts of congenital complete heart block as reported in American literature. In the cases reviewed by Yater and others it was found that syncope was not infrequent and cyanosis was observed in approximately one-half of the patients. On the other hand, dyspnea and evidence of congestive failure was conspicuously absent. The pulse rate was rarely under 40, usually being in the range of 50 or higher. The blood pressure was elevated in a few of the reported cases and ranged from 150 to 190 systolic and 90 to 100 diastolic. The A.V. block has been found to be partial or complete. A large number of patients followed have expired in early life and death was usually due to other malformations and not to the congenital heart block; however, the frequency of Adams-Stokes seizures in some patients increases the tendency to sudden death. In spite of many handicaps associated with congenital heart block there are patients who not infrequently survive to adult life and beyond. It has been generally observed that faulty growth may be present and stigmas such as club fingers are not uncommon.

As to the frequency of complete heart block in general, it was found to be present in only 108 cases of a total number of 13,211 cardiac cases studied by White,[9] Lemann,[10] Sprague[11] and others. White estimated that 90 per cent of the higher grades of heart block occurred in patients over fifty years of age. Of 10,000 patients studied at the Massachusetts General Hospital upon whom electrocardiograms were taken, there were only four patients who had complete heart block thought to be on a congenital basis.[12]

Mitchell et al.,[12] reviewed 17,862 deliveries at the Kings County Hospital during a five year period and found that there had been only one patient who had manifestations of complete heart block. These authors considered this patient to have a congenital type of heart block and stated that most patients with heart block who become preg-

nant have a congenital anomaly as the basis for the conduction defect.

When one considers the above figures it seems obvious that pregnancy will occur rarely in an already relatively rare condition. Walz[13] in 1922 reported the third authentic case of pregnancy in a patient with congenital complete heart block. In 1930, Herrmann and King[14] described a patient who had complete A.V. block since the age of twenty and a record of six successful deliveries without complications. The heart block in this patient was thought to be on the basis of rheumatic fever.

Bernstein[15] reviewed the literature up to January 1, 1936, and found only six recorded cases of complete heart block in which pregnancy with successful delivery had occurred. Bernstein reported a case of a twenty-three year old primipara, who after thirty-six hours in labor without progress, was subjected to cesarean section under local anesthesia. The puerperium was uneventful. The patient was found to have serologic evidence of syphilis and the cardiac lesion was ascribed to this etiologic agent.

Jensen[13] states in his text, 1938, that sixteen other cases have been published in some detail and Nest[13] mentioned three additional case reports. There have been other reports[16] from time to time, bringing the total up to approximately twenty-six.

Mitchell et al.,[12] in 1943, reported a case from the Kings County Hospital of a twenty-three year old primipara with complete congenital heart block who experienced normal pregnancy, normal delivery and uneventful recovery. The heart block in this patient was present one year later. Mitchell,[12] Bernstein[15] and others have emphasized that the prognosis in these cases is good because the myocardium is unimpaired. It is the opinion of these writers and of most investigators that delivery should be as usual and that interruption of pregnancy and sterilization procedures are not justified.

CASE REPORT

A twenty-one year old, white housewife was seen on September 17, 1940, because of an acute respiratory infection. She had been healthy all her life and had experienced only the usual childhood diseases, with an occasional sore throat. At the age of eleven she had an episode of tonsillitis which kept her in bed for approximately one week. She returned to school and her dancing lessons and recalled no unusual fatigue. She became an acrobatic dancer and had never experienced unusual breathlessness or fainting. Menarche was established at the age of thirteen and was regarded as of normal pattern. During her second or third year of college, at about the age of seventeen or eighteen, the school physician remarked that her pulse was slow. She continued active physical exercises and acrobatic dancing. At eighteen her appendix was removed and at the age of nineteen a tonsillectomy was done.

Her height was 5 feet 5 inches and she weighed 116 pounds. She was well developed and except for the findings referable to her heart, physical examination revealed no abnormalities. The apex beat was in normal location and no thrill was felt. Percussion of the heart borders disclosed no enlargement. A soft systolic murmur was heard over the entire precordium, most distinctly over the third left rib near the sternum. Her pulse rate was in the forties. Auricular contractions were audible between ventricular systoles. Her blood pressure was 110 systolic and 70 diastolic. Blood studies were normal. Urinalysis and serology were entirely normal. An electrocardiogram revealed complete A.V. dissociation. Auricular rate varied between 72 to 82, while the ventricular rate was 52 to 64. The QRS complexes were normal and there was a normal axis deviation. T waves were positive in lead I, negative in leads II, III and IVF.

At the age of twenty-two she became pregnant. She progressed with no more than the usual discomfort and at term, after twelve hours labor, was delivered of a 6½ pound normal infant. At the height of labor, her pulse had increased to 64 but later this promptly subsided to the high forties where it remained during an uneventful puerperium.

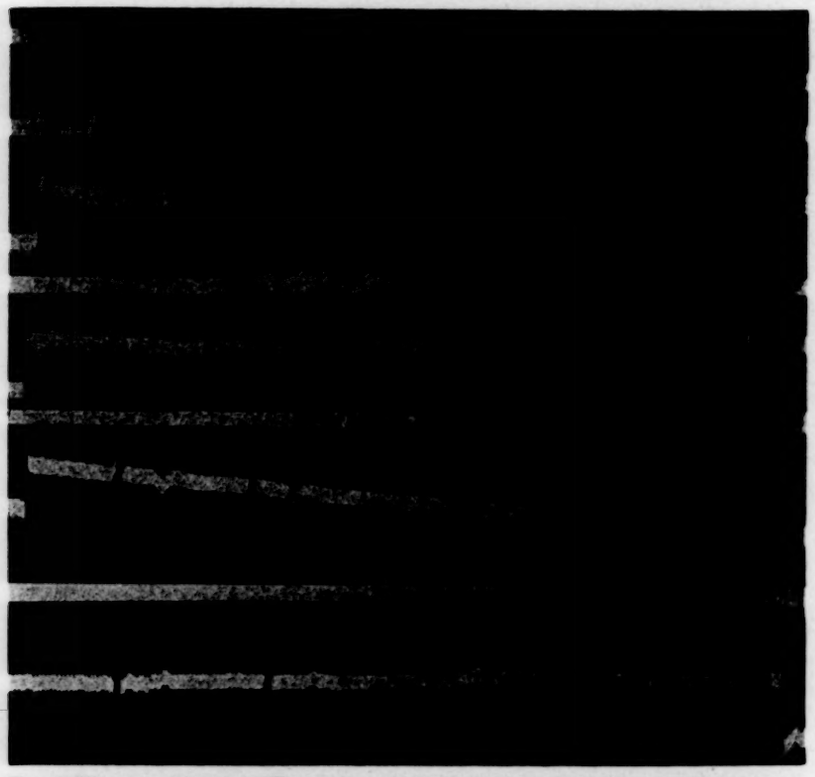


FIG. 1. Electrocardiogram, December 12, 1945, showing complete A.V. dissociation.

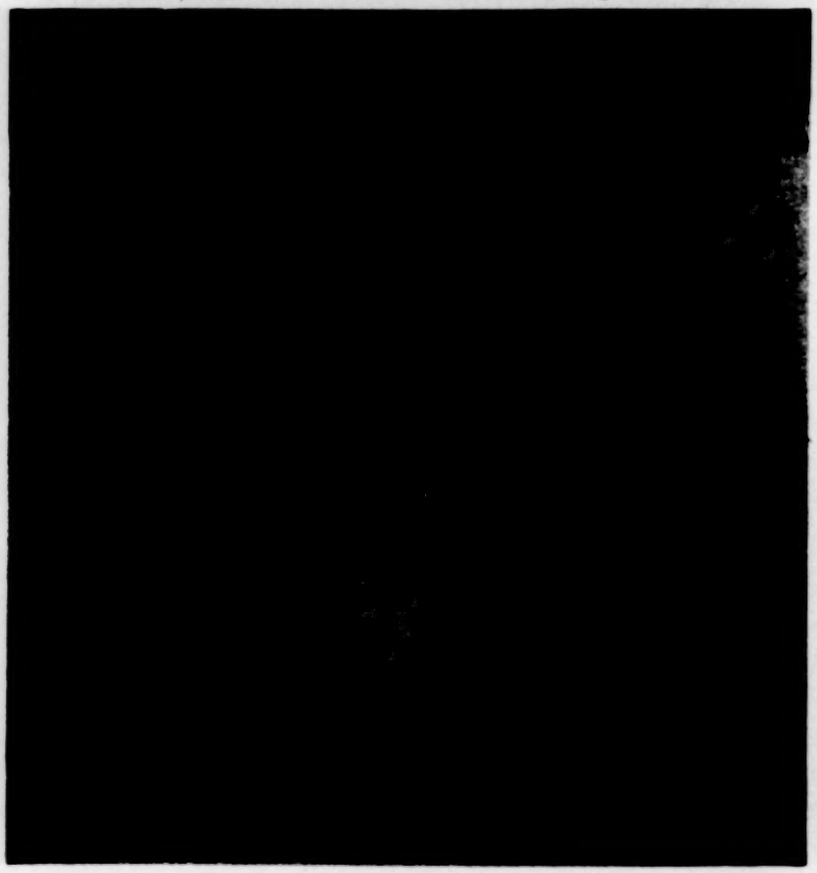


FIG. 2. Teleroentgenogram showing slight generalized enlargement of heart.

She has remained in good health and was recently seen in the eighth month of her second pregnancy. A recent teleroentgenogram showed a slight enlargement of the right and left ventricle. Subsequent electrocardiograms have continued to show 2 to 1 A.V. dissociation. An ECG taken on December 12, 1945, demonstrated an auricular rate of 64 to 66 with a ventricular rate of 40 to 42. The T waves were negative in leads III and CFIV.

While one might question this case as satisfying all of Yater's criteria for congenital block (a slow pulse was not discovered until she was seventeen or eighteen years of age) we think it fits that classification. An illness at eleven years of age was present; however, the patient recalls promptly returning to school without a period of convalescence. We doubt that she suffered an endomyocarditis at this time and recovered so completely and promptly. The systolic murmur probably represents an interventricular septal defect. We believe this to be a case of congenital complete heart block in a patient who experienced normal pregnancy, uncomplicated delivery and uneventful recovery.*

SUMMARY

In summary we wish to emphasize the relatively infrequent occurrence of acceptable cases of congenital complete heart block as reported in American literature. A review of the literature reveals that only twenty-six cases of complete heart block in pregnant women have been reported.

A report of a patient with congenital complete heart block who experienced normal pregnancy and uneventful recovery has been presented. This report adds emphasis to the current belief that patients with complete heart block who become pregnant should be allowed to continue a normal pregnancy, provided that the associated congenital defects do not constitute an indication for therapeutic abortion.

It is our hope that the report of this case of congenital complete heart block in pregnancy may stimulate interest in this rare condition and ultimately lead to better understanding and proper recognition of this entity.

* Since this paper was delivered, this patient, on July 16, 1946, delivered a healthy 7 lb. male infant. Convalescence was uneventful.

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Special Feature

Southern Society for Clinical Research

SECOND ANNUAL MEETING, NEW ORLEANS, JANUARY, 1948

Presidential Address

The Middle Zone in Medicine

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If one were still young enough to be valorous, a presidential address would offer the chance to illustrate the dictum that "young men are fitter to invent than to judge, . . . fitter for new projects than for settled business," and to present a scientific discussion of recent investigative work. One old enough to be discreet would probably make no speech at all, realizing that "even a fool, when he holdeth his peace, is counted wise." He who, like myself, is neither young enough to retain valor nor yet old enough to have achieved discretion, will be tempted to philosophic discourse and, pretending to disdain both the hectic energy of youth (as Brownian movement) and the professorial calm of age (as atrophy of imagination), will discuss "Whither are we tending?" and "the evils of the times" as though endowed with an understanding which he has not.

The remarks to follow are directed toward all of us who teach clinical medicine, and are based on the belief that in many of our better schools research is outstripping teaching, and are for the purpose of urging that we preach what we practice. This Phillipic (without eloquence) is therefore aimed at the general concepts of disease which we allow to develop in the minds of our pupils.

To say that most of our progress during the nineteenth century, and much of it in the twentieth, developed from the deadhouse and hence originally stems from the ancient Egyptian embalmers is to state a truism. It is equally trite to point out that much of our progress in recent years has come from a better understanding of the rôle of emotional disturbances in the production of symptoms, and hence may be traced back to primitive man and his concepts of infestation by evil spirits. Clinical teaching of today is often based largely on the assumption that patients either have, on the one hand, demonstrable structural disease or, on the other hand, functional disorders dependent on emotional disturbances. Many of our able clinicians, failing to find an organic ailment and observing that the patient is somewhat anxious and disturbed (as most patients are), refer the problem to the psychiatrist, acting on the principle that "words are the physicians of a mind diseased." Any lingering doubts based on some subconscious dissatisfaction with either the structural or emotional interpretation of the nature of the symptoms are likely to be met by adding the label "psychosomatic," without pausing to consider that a name does not necessarily constitute an explanation and that a useful concept deserves a better fate than to become a scrap basket for our ignorance.

It is my opinion that such a conception of the causation of symptoms is accurate in so far as it goes but is decidedly incomplete, and that when we practice it with our patients or foster it in our students we err in the sense that "a wrong doer is often a man that has left something undone, not always he that has done something." One does not have to be a Prometheus to have his liver picked at; and at the risk of exposing mine to the onslaughts, not of vultures, but of more predatory birds (pathologists and psychiatrists), I wish to urge that our clinical stool have a third leg, without which the other two are often as useless as Icarian wings that melt in the sun.

One objection to the structural-emotional dualistic conception of the cause of symptoms is its relative therapeutic nihilism. A large proportion of structural disorders are irreversible, at least at the present time. Some few emotional

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ills are irreversible; more can be successfully treated, but many of these can be expected to respond only to prolonged and necessarily expensive psychotherapy.

A more compelling objection to this dualistic concept is its failure to account for the symptoms in a large proportion of our patients. Abdominal pain will serve as an apt illustration. The most common cause of this symptom is neither structural disorder nor emotional upset but quantitative or qualitative dietary indiscretion. Such common and important causes of abdominal discomfort as acute appendicitis and friction with in-laws are less frequent than being "crammed with distressful bread," while peptic ulcer and trouble with the boss assume secondary rank when compared with the ingestion of one man's poison which is another man's meat. Such abdominal pains are neither emotional nor structural; they belong to the middle zone of somatic functional disorders.

To illustrate this thesis with other common symptoms we may consider syncope and faintness. The most frequent causes of these symptoms are not such structural disorders as cerebral neoplasm or islet cell tumors, nor yet such a common emotional disturbance as vasovagal syncope, but rather the non-psychogenic functional group of disorders such as idiopathic epilepsy, carotid sinus syncope, paroxysmal tachycardia, postural hypotension resulting from prolonged bed rest and hypoglycemia consequent to faulty dietary habits. Here again, among the most common causes of important symptoms we have conditions which can neither be assigned to the realm of an emotional Ariel nor to the kingdom of a structural Caliban; they belong to the middle zone.

The point at issue may perhaps be strengthened by citing a specific case: A thirty-seven year old woman developed recurrent headaches of increasing frequency and severity. These began a few months after the death of a brother to whom she was devoted. After several weeks the seizures were complicated by the presence of outspoken vertigo. Examination revealed unilateral impairment of hearing and evidence of depression which the patient attributed to the headaches. She was seen by several internists, an otolaryngologist, a neurologist, a neurosurgeon, an allergist and a psychiatrist, all of whom were unusually competent. Opinions were divided as to whether cerebral neoplasm or emotional disturbance was the cause of the symptoms. As a temporizing measure she was given a trial on elimination diets which she followed carefully, except for continuing to take coffee of which she was very fond. The symptoms continued. Several weeks later coffee was withdrawn and all manifestations except the deafness abruptly ceased. After seven years of complete freedom from headache the patient drank two cups of coffee at about 10 A.M. At 6 P.M. a severe headache set in. Ergotamine produced prompt relief of the headache but after about one-half hour severe substernal pain associated with fear of impending death occurred. When she was seen an hour later by two physicians, the possibilities of myocardial infarction and of an anxiety reaction were considered. In the light of the possibility that the pain might conceivably be the result of coronary constriction, induced by ergotamine, nitroglycerine was administered. Within five minutes the pain and anxiety were completely relieved and have not recurred, despite vigorous physical exertion and considerable emotional stress.

This patient had at different times two symptoms: headache and constrictive chest pain which could readily have been ascribed either to structural disorder or to emotional disturbances. In both instances non-psychogenic functional disorders were responsible.

Those of you with an historical bent, mindful of my present abode, will naturally wonder what the shooting is about, while those with literary inclinations may be tempted to reflect that the most popular Elizabethan drama in the most spacious state is "Much Ado about Nothing," and all of you may agree that there can be little significance in emphasizing something which we all practice daily in our investigative work, namely, the study of the somatic mechanisms involved in the production of symptoms. Actually, we often do not preach that which we practice. Since the application of chemistry and physics to the study of disease is a relatively new phenomenon, we cannot expect the middle-aged physician to be steeped in this "physiolosomatic" approach to disease. However, when our recent graduates and students persist in the dualistic structural and emotional approach and display, as nearly all do, no evidence of understanding the middle zone of non-psychogenic functional disorders as the third and often most important leg of the stool, one is forced to conclude that we who teach clinical medicine, and who are far from ignorant of the significance

of this group of disorders, are failing to impress such knowledge upon the minds of our students. It would seem to be the special function of those who teach internal medicine and pediatrics to temper alike the harsh structural winds of pathology and surgery and the soft seductive emotional zephyrs of psychiatry, with the cool, clean air of clinical physiology if a healthy intellectual climate is to be achieved for our pupils.

It has already been stated that the modern concept of the great importance of emotional conflicts as causes of symptoms may be considered as having been derived from primitive man and his concern with evil spirits, while the structural approach to disease can be traced via the dead house to the early Egyptian embalmers. In emphasizing the middle zone are we forsaking history for hysteria, or can we assign to this concept also a respectably ancient origin? One need not seek far to find that the clearest thinkers of antiquity, the Greeks, were reasoning in such terms when they ascribed disease to disturbances in the four humors, a concept of disease which is based neither on structural change nor on emotional disturbance but rather on the middle zone of nonpsychogenic functional disorders. These several ancient approaches, each containing a germ of truth, are separately inadequate, but when integrated furnish a firm basis for clinical thinking. To provide such a synthesis is one of the chief tasks of modern clinical teaching. Such teaching, like any other, can be effective only if it stems from example. If we wish our pupils to study the known, we, their teachers, must light their paths by studying the unknown. A society such as this one may, over the long pull, actually accomplish as much good through its inevitable by-product, better teaching, as through its immediate objective, the encouragement of research. In furnishing such encouragement we shall refuse to allow the shocking results of the recent advances in nuclear physics to force us to accept the eccliastic proverb that "He that increaseth knowledge increaseth sorrow," but shall adopt a long-term viewpoint and, endorsing that fermentative spirit which is a prerequisite for research, follow the prophecy of Daniel that, "Many shall run to-and-fro and knowledge shall be increased."

Abstracts of Southern Society for Clinical Research

SECOND ANNUAL MEETING, NEW ORLEANS, JANUARY, 1948

PROCEEDINGS

(Read by presentation)

1. HYPOKALEMIA MASKING THE SYMPTOMS OF HYPOCALCEMIA

FRANK L. ENGEL, M.D. *and (by invitation)* SAMUEL P. MARTIN, M.D.

From the Department of Medicine, Duke University School of Medicine, Durham, N. C.
(We are indebted to Dr. H. M. Taylor of the Department of Biochemistry for the chemical analyses in this study.)

Two patients with hypocalcemia and hypokalemia due to chronic diarrhea, one complicated by diabetic coma, have been observed. One suffered from non-tropical sprue, the other from probable pancreatic insufficiency. Both were observed clinically during periods in which they exhibited preëminently hypocalcemic tetany or hypokalemic paresis. During both phases the serum calcium was consistently below 6.5 mg. per cent but tetany was apparent only when the serum potassium was above approximately 2.5 mEq/L. Paresis appeared at the same Ca levels when the potassium fell below approximately 2.0 mEq/L. In one patient simultaneous measurements of serum calcium and potassium, electrocardiograms and studies of nerve-muscle irritability were carried out during intravenous administration of potassium and calcium salts. During the hypocalcemic-hypokalemic phase with paresis administration of potassium produced a decrease in chronaxie with marked clinical signs of tetany as the serum potassium rose, the serum calcium remaining relatively constant. These effects were reversed either by the spontaneous decline in potassium after discontinuing infusion or by administration of calcium before potassium levels had fallen to the initial low level. Measurements of serum sodium, chloride, CO_2 combining power, phosphate, total protein, albumin and globulin were made at appropriate intervals. These data suggest that potassium depletion may be a reason for the not infrequent failure to develop clinical tetany despite hypocalcemia in steatorrhea and emphasize the need for caution in treating this hypokalemic syndrome with intravenous potassium salts.

2. STUDIES ON DICUMAROL IN HUMAN BEINGS; ITS NEUTRALIZATION BY VITAMIN K_1 OXIDE, MENADIONE BISULFITE, SYNKAYVITE AND BLOOD

DAVID F. JAMES, M.D., IVAN L. BENNETT, JR., M.D., PERITZ SCHEINBERG, M.D. *and* JOHN J. BUTLER, M.D. *(introduced by Arthur J. Merrill, M.D.)*

From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

The impression that dicumarol toxicity can readily and consistently be controlled by the intravenous administration of 64 mg. menadione bisulfite is widespread but based on a relatively small number of reported observations. In order to establish a broader clinical basis for the control of dicumarol action, menadione bisulfite in 64 mg. and larger amounts were given to patients whose prothrombin times were prolonged by dicumarol to within the range where spontaneous bleeding has been noted. The action of menadione bisulfite was compared with that of vitamin K_1 oxide, synkayvite and fresh and bank blood.

One hundred one patients were given dicumarol in the usual dosage. When the prothrombin time exceeded that of control plasma diluted to a concentration of 20 per cent, the patient was either allowed to return untreated to his normal prothrombin level or was given large single doses of the substances mentioned above. Blood samples taken at frequent intervals during the succeeding twenty-four hours, and daily thereafter, were studied for prothrombin activity.

Vitamin K_1 oxide was markedly superior to the other substances tested. The prothrombin time of patients given 0.5 Gm. or more of this material intravenously required an average time of thirteen hours to arrive and stay within safe limits (i.e., at thirteen hours the patient's prothrombin time was as short as or shorter than that of 30 per cent normal control plasma).

3. Effect of Combining Vasoconstrictors with Local Anesthetics upon the Duration of Spinal Anesthesia in Man

Kenneth Bray, M.D., S. Katz, M.D. (*by invitation*) *and* J. Adriani, M.D.

From the Department of Surgery, Louisiana State University School of Medicine, New Orleans, La.

The usefulness of epinephrine in prolonging the action of local anesthetics for infiltration, nerve block and topical use has been established. Relatively speaking, other vasoconstrictors are nowhere as effective. The usefulness of epinephrine intrathecally is not accepted, as its effectiveness is controversial. Recent reports based mostly upon clinical impression have added confusion to the issue and no controlled studies are available in man.

In this study patients requiring spinal anesthesia four and five times in succession were used. Three hundred observations were made using a short acting drug (procaine), an intermediate acting preparation (pontocaine) and a long acting drug (nupercaine) alone, twice in succession. In subsequent administrations the effect of adding epinephrine, ephedrine and neosynephrine upon intensity and duration of action were compared with results in the controls.

4. Urecholine in the Treatment of Motor Abnormalities in the Gastrointestinal Tract of Neurogenic Origin

R. W. Rundles, M.D. *and* George J. Baylin, M.D. (*introduced by Eugene A. Stead, Jr., M.D.*)

From the Department of Medicine, Duke University School of Medicine, Durham, N. C.

Gastric dilatation with prolonged retention of food and secretion has been a major postoperative complication of vagotomy. Twenty-two patients with this complication were treated with urecholine (urethane of B-methylcholine chloride). Of the parasymphatheticomimetic drugs urecholine appears to be the most effective as well as least likely to cause side reactions. Within three to five minutes after hypodermic injection of 5 mg. of the drug, vigorous peristaltic activity developed and was usually effective in emptying the stomach. Oral administration of the drug in doses of 10 to 50 mg. was effective in some patients. Transit of barium through the jejunum was hastened, the caliber of the intestine decreased and mucosal pattern became less coarse.

Disorganized gastrointestinal activity with gastric retention in spite of free passage of barium into the upper intestinal loops occurs in some patients with diabetic neuropathy. In three such patients urecholine was effective in promoting gastric emptying and restoring normal intestinal motility as judged roentgenologically and by disappearance of clinical symptoms.

Three patients with megacolon were treated with oral doses of urecholine for periods of eight to twelve months. Bowel habits became normal and there was complete freedom from clinical symptoms.

5. Clinical Description and Chemical Pathology of the Syndrome of Familial Idiopathic Dysproteinemia

F. Homburger, M.D., N. F. Young, M.D., Mary L. Petermann, M.D. *and* Edward C. Reifenstein, Jr., M.D.

From the Departments of Clinical Investigation and Protein Chemistry, the Sloan-Kettering Institute for Cancer Research, Memorial Cancer Center, New York, N. Y.

Four of six members of one generation in the same family were found to have an abnormal distribution of protein components in the blood plasma; although only two of the four had gross hypoproteinemia, all four had clinical manifestations, particularly edema. In the females the dynamics of peripheral circulation were disturbed. Detailed studies have eliminated the usual causes of disturbances of the circulating protein components. Electrophoretic, immunologic and chemical studies of the plasma proteins were undertaken in an effort to clarify the pathogenesis of this disturbance. Data will be reported on the rate of disappearance of circulating injected human albumin and the rate of restoration of circulating protein following plasmapheresis. The significance of some of the findings will be discussed.

6. Aspects of the Biologic Decay Periods of Sodium in Normal and Diseased Man

Sam Threefoot, M.D., (*by invitation*), George Burch, M.D. *and* (*by invitation*) Paul Reaser, M.D.

From the Department of Medicine, Tulane Medical School and Charity Hospital, New Orleans, La.
(Aided by a grant from the Life Insurance Medical Research Fund, the War Contract No. W-49-007-MD-389, the Helis Institute for Medical Research and the Mrs. E. J. Caire Fund for Research in Heart Disease.)

A knowledge of the duration of time for which a radioactive element is retained in the body has important significance physiologically in safety considerations and in dosage calculations in tracer studies and isotope radiation therapy. The biologic decay-life of sodium in man can be determined satisfactorily with the long half-life Na^{22} ($T\frac{1}{2}$ = 3 yr.) but not with Na^{24} ($T\frac{1}{2}$ = 14.8 hr.). During the course of experiments Na^{22}, with an activity of such that 10,000,000 to 17,725,000 disintegrations occurred per minute, was injected into each subject. A daily blood serum concentration of Na^{22} was determined for from thirty to sixty consecutive days. All samples of urine were collected separately and the Na^{22} excretion determined for each. The subjects consisted of four control subjects free from cardiovascular and renal disease, six subjects with chronic congestive heart failure (two were slowly improving, two rapidly improving and two becoming worse) and two subjects with chronic glomerulonephritis of the nephrotic type.

Since only the serum concentration of Na^{22} and the rate of urine excretion of the radioelement were measured, it was not possible to know the time required to excrete one-half of the injected Na^{22}, the biologic half-life period($B\frac{1}{2}$), *per se*. Therefore, it was necessary to introduce the following terms:

(1) $C\frac{1}{2}$ = time required to reduce the serum concentration to one-half the value obtained at any time after equilibrium between the Na^{22} and Na^{23} of the body has been reached.
(2) $U\frac{1}{2}$ = time that would be required to eliminate in the urine one-half of the administered Na^{22}.

The results are briefly summarized by Table 1. It can be seen that with the exception of Subject No. 2 the $C\frac{1}{2}$ periods were less than the $U\frac{1}{2}$ ones. This is to be expected because of the influence of other factors, such as other avenues of sodium excretion, shifts of sodium within the sodium compartments of the body and variations in the volume of these compartments. The subjects with chronic congestive heart failure and those with chronic glomerulonephritis of the nephrotic type had $C\frac{1}{2}$ and $U\frac{1}{2}$ periods which were longer than those of the controls. (Table 1.) Sodium and water diuresis in the

Table 1
CONTROL

Subject No.	$C\frac{1}{2}$	$U\frac{1}{2}$	Days of Continuous Observation	Weight Change (Pounds)
1	14	30	62	− 3.5
2	13	9	22	−14
3	12	42	45	−11
4	14	34	65	+ 2.3
Mean	13.3	28.8	48.5	− 6.6
Congestive Heart Failure (Slowly Improving)				
5	40	60	35	−18
6	42	72	46	− 7
Mean	41	66	40.5	−12.5
Congestive Heart Failure (Rapidly Improving)				
7	13	26	62	−29
8	28	33	58	−17
Mean	20.5	29.5	60	−23
Congestive Heart Failure (Slowly Becoming Worse)				
9	24	72	68	+17
10	30	48	58	− 5.5
Mean	27	60	63	+ 5.8
Chronic Glomerular Nephritis (Nephrotic Type)				
11	58	660	45	+15
12	54	366	71	−86
Mean	56	513	58	−35.5

Summary of Results. The $C\frac{1}{2}$ value indicates time in days required for the serum Na^{22} concentration to reach one-half the initial equilibrium concentration. The $U\frac{1}{2}$ values represent the time in days required for one-half of the total Na^{22} injected to be eliminated by the urine.

subjects whose congestive heart failure rapidly improved resulted in a definite shortening of the $C\frac{1}{2}$ and $U\frac{1}{2}$ periods, the times becoming even less than that for the normal subjects on high sodium intake. The $C\frac{1}{2}$ periods in the control subjects were essentially the $B\frac{1}{2}$ periods. This is less likely to be true for the abnormal subjects.

The $C\frac{1}{2}$ and $U\frac{1}{2}$ periods were affected by measures which influenced sodium metabolism and excretion such as sodium intake, desoxycorticosterone acetate, mercurial diuretics, water intake, pitressin and others.

These experiments have shown that the $B\frac{1}{2}$ as well as the $C\frac{1}{2}$ and $U\frac{1}{2}$ for sodium are quite variable, being influenced not only by normal physiologic phenomena but particularly by disease and drugs. These variations must be taken into consideration when calculating the safety doses for radiosodium. $C\frac{1}{2}$ and $U\frac{1}{2}$ periods found for Na^{22} indicate the length of time required to turnover Na^{23} in men. These experiments will be published in detail elsewhere.

7. Urinary Thyrotropic Hormone as a Diagnostic Test in Primary Hypothyroidism and in Evaluation of Therapy in Diseases of the Thyroid Gland—a Preliminary Report

James A. Greene, M.D. (*by invitation*) Don W. Chapman, M.D. *and* Lynn Bernard, M.D.

From the Department of Medicine, Baylor University College of Medicine and Hermann Hospital, Houston, Texas.

The urinary thyrotropic hormone excretion has been ascertained in four cases of myxedema before thyroid therapy and in five before and following thyroid therapy for periods from six to eighteen months. In addition, the thyrotropic hormone excretion has been ascertained in the urine of nineteen patients with classic hyperthyroidism before therapy and in five of them following effective thiouracil therapy. The hormone assay was carried out according to the method of Parks and day old chicks were used as the test animal.

Active thyrotropic hormone was present in the urine in all subjects with myxedema before treatment and the amount diminished or disappeared following thyroid therapy. The active hormone was present in the urine of only one subject with hyperthyroidism before therapy and appeared in all patients following effective treatment with thiouracil. The possible significance of these findings to the physiologic relationship of the thyroid and pituitary glands and their diagnostic and therapeutic evaluation will be discussed.

8. Pteroylglutamic Acid Balance Studies on Monkeys

Paul L. Day, M.D. *and* (*by invitation*) Dorothy Sue Gaines, M.D., Marion McKee, M.D., Phyllis Scroggin, M.D. *and* Raymond Houchins, M.D.

From the Department of Biochemistry, School of Medicine, University of Arkansas, Little Rock, Arkansas.
(Aided by a grant from the Nutrition Foundation, Inc.)

Young rhesus monkeys were housed in individual steel metabolism cages and given a diet known to produce anemia, leucopenia and pteroylglutamic acid deficiency. The diet was supplemented with the amounts of PGA (pteroylglutamic acid) indicated below for periods of twenty-one to twenty-eight days. Daily urine and feces collections were made, and were analyzed for PGA using Streptococcus faecalis. When the diet was supplemented with 100 micrograms of PGA daily, the average daily output in micrograms was as follows: urine, 5.2; feces, 7.3; total, 12.5. When the daily dietary supplement of PGA was increased to 1 mg. the output in micrograms was: urine, 21.8; feces, 9.6; total 31.4. When the diet was supplemented with Difco yeast extract in an amount to furnish approximately 100 micrograms of PGA, largely in the form of PGA conjugate, preliminary data showed an output as follows: urine, 2.05; feces, 19.7; total 21.8. It is thus evident that when the level of intake of PGA is at the minimum daily requirement (100 micrograms) the total output in excreta is only about 12 per cent of the intake. A ten-fold increase in intake results in less than a threefold increase in output. Preliminary data indicate that the conjugate of PGA is not completely absorbed by the monkey.

9. Treatment of Neoplasms by the Direct Infiltration of Radioactive Colloidal Metallic Gold

P. F. Hahn, M.D.

From the Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee

Radioactive Au^{198} having a half-life of 2.7 days has a number of unique properties which

recommend it for use in tumor therapy. Having one of the best cross sections to thermal neutron flux, it is economically prepared in the uranium pile. The insolubility of colloidal metallic gold in body fluids enables one to set up millions of uniformly dispersed focal sources of beta radiation in discrete tumor masses or metastatic lesions causing a minimum of encroachment on neighboring normal structures in contrast to radiation from radium, radon or x-ray. Preliminary use in readily accessible tumors subject to follow-up inspection will be described. The potentialities in conjunction with surgery in the therapy of deep seated neoplasms will be considered. Present limiting factors in the exploitation of this valuable isotope are: (1) lack of knowledge of the various human tissue tolerances for beta radiation; (2) ignorance of various tumor sensitivities to this radiation and (3) relatively few experienced qualified investigators and therapists in this field.

10. Fractionation and Chemical Analyses of a Malignant Mouse Thymoma

Thomas N. Warren, M.D. (*introduced by Alfred Chanutin, M.D.*)

From the Biochemical Laboratory, University of Virginia, Charlottesville, Va.
(This work was supported by a grant from the National Institute of Health and the National Cancer Institute.)

After subcutaneous transplantation of tumor cells into dba_{212} mice, the animals survive about three weeks and shortly before death the tissue is grossly necrotic; at the end of two weeks this tumor is quite large and is classified as "healthy." The tumor tissue was treated so that (a) the stroma, (b) the tumor cells and (c) the cell-free saline extract were obtained. Each of these main fractions was further fractionated with the aid of ethanol and cold. All of the eleven subfractions were analyzed for total lipide carbon, total cholesterol, total phospholipides, total nuclei acids and desoxyribosenucleic acid.

Data will be presented for the fractions of fourteen-day ("healthy") and the twenty-day (necrotic) tumor tissues. The outstanding differences between these two groups are the decreased neutral fats or fatty acids and the increased total cholesterol in the necrotic tumor. Each subfraction has a characteristic and distinct chemical composition.

The data for the thymomas of mice treated with urethane and a nitrogen mustard and mice fed on a choline-enriched diet will be shown. The growth of the tumor at the end of twenty days in mice treated with urethane and HN2 was greatly inhibited, but the percentage concentrations of the various constituents were not markedly affected. Choline exerted very little effect on either the size or chemical composition.

From these data it would appear that the inhibition of tumor growth is not reflected by changes in the chemical composition of the tissue.

11. Morphologic Studies in Syphilitic Lesions during the Herxheimer Reaction

Walter H. Sheldon, M.D. *and* Albert Heyman, M.D. (*introduced by Paul B. Beeson, M.D.*)

From the Departments of Pathology and Medicine of Grady Memorial Hospital and the Emory University School of Medicine, Atlanta, Ga.

The occurrence of the Herxheimer reaction in the treatment of syphilis has long been recognized but its mechanism has never been thoroughly investigated. Although the syphilitic lesions during this reaction frequently show gross changes, these have never been observed morphologically.

We have made histologic studies of the cutaneous and mucosal lesions during the Herxheimer reaction in series of patients with secondary syphilis. Definite morphologic changes occur during this reaction. They consist of congestion, edema, alteration of the vascular endothelium and acute inflammatory cell infiltration. These changes are confined strictly to the syphilitic lesions and disappear within six to eight hours. These histologic findings were observed in practically all patients with clinical evidence of the Herxheimer reaction. The same changes probably occur in the Herxheimer reaction of the cardiovascular and central nervous systems and may account for the serious clinical complications which are occasionally encountered.

Our studies suggest a similarity between the Herxheimer reaction and the tuberculin reaction and further investigation comparing these two phenomena may lead to a better understanding of some of the immunologic aspects of syphilitic infection.

12. Effect of Benadryl and Thorotrast on Experimental Anaphylactic Shock

Andres Goth, M.D. *and* James Holman, M.D.
(*introduced by Arthur Grollman, M.D.*)

From the Department of Pharmacology, Southwestern Medical College, Dallas, Texas.

The purpose of these experiments was to study the mechanism of the anaphylactic reaction and the site at which it takes place.

A series of twenty-one dogs were sensitized to horse serum. A few minutes prior to the shocking injection either benadryl—10 mg. per Kg.—or thorotrast—2 to 6 cc. per Kg—was. injected intravenously. Five dogs received no pretreatment and served as controls. Blood pressure and clotting time were measured in all dogs before and after the shocking injection.

The results indicate that benadryl had only a slight effect in preventing the fall of blood pressure and it failed to prevent the incoagulability of the blood. On the other hand, large doses of thorotrast prevented both of these manifestations of anaphylactic shock.

These results can be best interpreted by saying that benadryl acts only as an antihistamine without affecting the fundamental process in the anaphylactic reaction, whereas thorotrast must have prevented the fundamental reaction from taking place. The latter drug could have accomplished this effect (a) by preventing the antigen from reaching the antibody or (b) by blocking the fundamental reaction which leads to the liberation of histamine and heparin. Since thorotrast is a powerful blocking agent of the reticulo-endothelial system the results of this study suggest that the reticulo-endothelial system plays an important rôle in anaphylactic shock.

13. Relationship Between the Value for the Resting Cardiac Output and the Symptoms of Congestive Heart Failure

Eugene A. Stead, Jr., M.D.

From the Department of Medicine, Duke University School of Medicine, Durham, N. C.
(This work was supported by a grant from the Life Insurance Medical Research Fund.)

The relationship between the value for the resting cardiac output and the symptoms of congestive heart failure is a complex one. Patients at the time of admission to the hospital will fall into the following groups:

1. Cardiac output low with failure and remains low with the disappearance of symptoms. Symptoms will be relieved by sodium restriction and continued use of diuretics. Majority of patients studied fall into this classification.

2. Cardiac output low with failure but increases with administration of digitalis or when complications such as pulmonary infarctions clear up; does not require salt restriction or diuretics when activity is reduced by bed rest.

3. Cardiac output normal with failure, remaining normal on compensation. Decompensation develops with increased activity. Cardiac output adequate at rest and symptoms at time of study present because of water-logging of the lungs which will persist until diuresis is completed.

4. Cardiac output high with failure, falls with compensation. This group includes: (1) restless, apprehensive, dyspneic patients whose outputs are adequate for rest but inadequate for mild exertion; (2) Patients with hyperthyroidism, anemia, arteriovenous fistula, patent ductus arteriosus, beriberi and certain infections.

14. Relationship Between Arterial Pressure and Renal Blood Flow

Harold D. Green, M.D. *and* (*by invitation*) Ben C. Ogle, M.D., J. Maxwell Little, M.D. Woodrow Batten, M.D., Carlos Rapela, M.D. (*Rockefeller Foundation Fellow*) *and* J. Roy Hege, Jr., M.D.

From the Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C.
(Supported by a grant from Life Insurance Medical Research Fund.)

A kidney and the distal stumps of the aorta and vena cava were progressively dissected free from a dog (kidney dog) until they were connected only by the proximal portion of the aorta and vena cava. A donor dog was heparinized and its femoral artery connected with the distal stump of the kidney dog's aorta. The distal stump of the kidney dog's vena cava was connected with an outflow meter. The proximal

stumps of the kidney dog's aorta and vena cava were then ligated and severed, thus completing the isolation of the kidney without its being at any time subjected to ischemia. The perfusion pressure was varied by a suitable clamp on the femoral artery of the donor dog, the pressure being lowered for one-half to two minutes to a given level and then returned to the control pressure.

Control flows averaged 230 ml./min./100 Gm. of kidney (range 115 to 450) at arteriovenous differences of pressure of 120 mm. Hg.

Satisfactory plots of flow vs. A-V difference of pressure were obtained in seven experiments. Of these only one gave a curve concave to the pressure axis as described by Selkurt. Two were convex and the remainder were straight. All tended to intercept zero flow at approximately 20 mm. Hg pressure.

Conclusion. In the isolated kidney no evidence of autoregulation of flow was observed.

15. Relative Rates of Renal Excretion of Sodium and Chloride Ions in Normal, Hypertensive and Heart Failure Subjects

Andrew J. Crutchfield, M.D. (*introduced by J. Edwin Wood, Jr., M.D.*)

From the University of Virginia School of Medicine, Charlottesville, Va.

Certain clinical and laboratory evidence suggests that renal retention of the sodium ion ranks among the primary events in the pathogenesis of the edema of congestive heart failure. The rôle of other extracellular electrolytes (e.g., chloride), though considered to be of lesser importance, has received little attention.

Experiments have been done in this laboratory to compare the relative rates of excretion of the sodium and chloride ions. The patients studied were grouped as follows: (1) normal, twenty-eight; (2) hypertensive without heart failure or clinical nephrosclerosis, eighteen and (3) edematous and non-edematous heart failure, twenty-five. The load of sodium chloride injected intravenously as 5 per cent solution actually contained 3,930 mg. of sodium and 6,070 mg. of chloride.

The average figures for the per cent of the load excreted over the five hour experiment period were as follows:

	Na Per Cent	Cl Per Cent
(1) Normal	20.1	19.2
(2) Hypertensive	19.2	19.4
(3) Heart Failure	9.0	10.1

These data indicate that the kidney of the heart failure patient excretes both sodium and chloride less rapidly than does the kidney of either the normal or hypertensive subject. Sodium excretion appears to be retarded slightly more than is chloride excretion although the difference is of doubtful significance.

About one third of the hypertensives had been treated for several months on low sodium diets similar to the ones used in treating the heart failure subjects. The normal sodium and chloride excretion by these subjects indicated that this type diet did not lead to body fluid deficit of either of these ions. It can safely be assumed, therefore, that the small excretion of sodium and chloride by the heart failure subject gave a true index of the existing renal ability to excrete these substances rather than indicating body fluid deficit of these substances.

16. Effect of Human Serum Albumin on Renal Hemodynamics and the Tubular Extraction of Para-Amino Hippuric Acid

Walter H. Cargill, M.D. (*introduced by Eugene A. Stead, Jr., M.D.*)

From the Department of Medicine, Duke University School of Medicine, Durham, N. C.

(This work was supported by grants from the Life Insurance Medical Research Fund and the Anna H. Hanes Fund.)

The intravenous administration of human serum albumin has been shown to produce a diuresis in patients with nephrosis. This has usually been attributed to a rise in plasma protein level and increased oncotic pressure of the blood. In an attempt to determine the immediate effect of albumin administration on the kidney, we have measured the inulin and para-amino hippuric acid clearance in two patients with nephrosis, five subjects with normal renal function, two hypertensives and one patient with subacute glomerulonephritis before, during and after the rapid intravenous administration of 300 cc. of a 25 per cent solution

of human serum albumin. In seven of these subjects the actual renal plasma flow was measured by the ratio

$$\frac{\text{PAH Excretion}}{\text{Arterial PAH conc.-Renal Venous PAH conc.'}}$$

samples obtained from the right renal vein by catheterization being compared with simultaneous samples from the femoral artery.

The hematocrit fell in all subjects after albumin (average fall = 16 per cent of control) and the plasma protein concentration rose less than 1 Gm. per cent. In nine of the ten subjects an immediate increase in inulin (average rise 14 per cent) and PAH (average rise 37.4 per cent) clearances was found, with a fall in filtration fraction in every case. The PAH clearance was found not to be a valid measure of renal plasma flow, however, since the percentage extraction of PAH $\left(\frac{A_{PAH} - RV_{PAH}}{A_{PAH}}\right)$ fell after albumin in each of the seven subjects in which it was measured (average fall = 19.6 per cent). The increase in actual renal plasma flow after albumin (average 44.3 per cent) was therefore greater than would be indicated by the PAH clearance (average 33.9 per cent) and the fall in filtration fraction correspondingly greater. In a control series of eight normal subjects under basal conditions consecutive determinations of renal PAH extraction at ten to fifteen minute intervals for one to two hours have shown a maximum variation of ± 1.8 per cent from the mean for each individual.

An immediate increase in urine flow in all subjects and in chloride excretion in the four subjects in which it was measured was found. The two patients with nephrosis differed from the others only in showing a greater rise in filtration rate and less fall in filtration fraction.

17. Effect of Saline Catharsis on Urine Specific Gravity

Philip M. Tiller, Jr., M.D. *and* Ellison R. Cook, III, M.D.
(*introduced by Thomas Findley, M.D.*)

From the Department of Medicine, Tulane University School of Medicine, New Orleans, La.

Methods used in concentration tests of kidney function fail to produce a consistent effect on urine specific gravity unless the subject has undergone water deprivation for at least twenty-four hours. Even after such a long fast, wide variations have been observed in normal controls. A method capable of producing a consistent high elevation of urine specific gravity would be of value.

Observations of urine specific gravity have been made in normal subjects at fifteen minute intervals following administration of a sodium phosphate solution. In seven subjects the cathartic was administered thirty minutes after breakfast. Within two hours the mean urine specific gravity was 1.027. In eleven subjects the cathartic was given after an eight to twelve hour fast and the mean specific gravity in ninety minutes was 1.035, ranging from 1.030 to 1.039. In six series of observations in a single subject the urine specific gravity ranged from 1.034 to 1.039 at the end of 120 minutes.

It would seem that the rapid dehydration produced by saline catharsis is an effective means of increasing urine concentration and might prove a reliable test of renal function.

18. Effect of Oral Streptomycin and Phthalylsulfathiazole on Blood Phenol Concentrations and Survival in Experimental Uremia

J. R. R. Bobb, M.D., Stanley L. Wallace, M.D. *and* J. Maxwell Little, M.D. (*introduced by Harold D. Green, M.D.*)

From the Department of Physiology and Pharmacology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

Blood phenol (tyrosine standard) determinations were made daily on five mongrel dogs. On the second day oral phthalylsulfathiazole (0.5 to 0.6 Gm./Kg. per day in divided doses) was started. On the fifth day bilateral nephrectomy was performed. The dogs diet in from two to eight days postoperatively with phenol levels from 3.70 to 7.35 mg./100 cc.

A similar experiment was performed on four dogs using oral streptomycin* (0.48 Gm./day in divided doses). The dogs died two to three days postoperatively with phenol levels from 1.54 to 2.14 mg./100 cc.

On five control dogs blood phenol levels were determined for four days (1.05 to 2.19 mg./100 cc.). On the fifth day bilateral nephrectomy was done. These dogs died two to five days post-

* Kindly supplied by Dr. D. F. Robertson of Merck and Co., Inc.

operatively with determined phenol levels from 3.69 to 6.60 mg./100 cc.

Stool cultures showed that both drugs reduced gas-forming organisms.

There were no differences in the symptoms of uremia exhibited by the three groups of animals.

Conclusion. Intestinal organisms other than the coliform group were responsible for blood phenol production; blood phenol levels were of minor importance in producing the symptoms of experimental uremia.

19. Studies of Human Carbohydrate Metabolism by the Liver Catheterization Technic

Philip K. Bondy, M.D. *and* David F. James, M.D.
(*introduced by Paul B. Beeson, M.D.*)

From the Department of Medicine, Emory University School of Medicine and the Medical Service, Grady Hospital, Atlanta, Ga.

Animal experimentation has proved the importance of the liver in carbohydrate metabolism. Although clinical experience has tended to confirm in humans the findings of the physiologists in animals, direct observations relating to the rôle of the liver have not heretofore been possible in man.

By the use of the cardiac catheter technic one can obtain samples of blood from the hepatic veins. If simultaneous arterial and hepatic venous samples are analyzed for glucose, it is possible to determine whether the liver is extracting glucose from the circulation or breaking down glycogen to contribute glucose to the blood.

The data obtained show that under fasting conditions the human liver contributes glucose to the peripheral circulation. After the administration of glucose intravenously, the arterial glucose level exceeds the hepatic level, indicating that glucose is being stored. As the arterial glucose level drops, the hepatic venous level drops less rapidly until it again exceeds the arterial level, indicating that the liver is releasing glucose and "braking" the descending blood glucose curve.

When peripheral venous glucose levels are obtained, they are lower than the hepatic venous level at the peak of the glucose tolerance curve, indicating that the peripheral tissues extract a greater portion of glucose from the blood flowing through them than does the liver. In the absence of measurements of peripheral blood flow, however, it is impossible to determine whether a greater absolute quantity is removed.

As the glucose tolerance curve falls, the arterial level often falls below the peripheral venous level, thus showing that glucose is being contributed to the circulation by the peripheral tissues. This phenomenon probably arises from the back-diffusion of glucose from intercellular fluid as the blood level falls below that in the tissue spaces. The possibility must also be considered that part of the glucose may be contributed by skin, bone and other connective issues which, unlike muscle, contain phosphatase.

Blood inorganic phosphate was also determined during the glucose tolerance tests. After the injection of glucose there was a reduction of the phosphate level of the blood drawn from arterial, hepatic and peripheral venous sources. This reduction could not be related quantitatively to the glucose level or to the rate of change of the glucose levels.

By application of the liver blood flow technic described by Bradley et al. (*J. Clin. Investigation*, 24: 890, 1945), one can estimate the actual amount of glycogen deposited or broken down in the liver.

The possible application of the technic to the elucidation of problems of the rôle of the liver in amino acid and fat metabolism are discussed.

20. Estimation of the Hepatic Blood Flow and Splanchnic Oxygen Consumption in Heart Failure

J. D. Myers, M.D. *and* J. B. Hickam, M.D.
(*introduced by Eugene A. Stead, Jr., M.D.*)

From the Duke University School of Medicine, Durham, N. C.

(This work was supported by grants from the Life Insurance Medical Research Fund and the Anna H. Hanes Fund.)

The hepatic blood flow has been measured in a group of patients with cardiac decompensation using the bromsulphalein technic of Bradley et al. The hepatic arteriovenous oxygen differences and cardiac outputs by the direct Fick method were determined in the same patients.

The hepatic blood flows in cardiac failure have been found between 200 and 700 ml. per minute per square meter (normal range, 600 to 1200 ml.). The degree of reduction in flow is in proportion to the reduction in cardiac output,

the hepatic blood flow remaining a quite constant, and normal, percentage of the cardiac output (17 to 27 per cent). Reduction in hepatic blood flow could not be correlated with the level of right arterial or peripheral venous pressure.

Femoral arterial-hepatic venous oxygen differences in the group with cardiac failure ranged from 5.5 to 12.8 volumes per cent. In only one instance was the oxygen difference below 8 volumes per cent.

These values are to be contrasted with the normal range which is 4.0 to 5.8 volumes per cent. By multiplying the hepatic blood flow by the hepatic arteriovenous oxygen difference, the "splanchnic" oxygen consumption is estimated. In normal individuals this ranges from 26 to 56 ml. per minute per square meter. In the patients with cardiac decompensation the splanchnic oxygen consumptions varied from 26 to 50 ml. and represented the normal percentage (av. 26) of the total oxygen consumption.

21. Maximum Hepatic Clearance of Bromsulphalein (= Lm, Bromsulphalein) by Normal Patients and by Certain Patients with Hepatic Disease

G. R. Hawley, M.D. (*by invitation*), Alice Smith, M.D. (*by invitation*) *and* M. F. Mason, M.D.

From the Department of Pathological Chemistry, Southwestern Medical College, Dallas, Tex.

The technic previously described for determination of the maximum hepatic clearance of bromsulphalein (= Lm, bromsulphalein) by dogs (*Am. J. Physiol.* In press.) has been applied to human subjects. Lm (bromsulphalein) in a series of seven normal male subjects of various ages ranged from 13.6 to 16.4 mg./min./sq.M. surface area. Somewhat lower values (9.4 to 13.0, six subjects; 16.0 and 16.9, two subjects) were observed in a series of eight apparently normal subjects who, nevertheless, had a history of a previous illness accompanied by jaundice.

Some values for Lm in patients with frank hepatic disease are as follows: infectious hepatitis and homologous serum jaundice with bilirubinemia, 6.3 to 10.8; two weeks to two months postbilirubinemic phase, 10.8 to 14.3; elemental phosphorus poisoning, acute phase, 6.7; twenty-nine days later, asymptomatic, 10.0; Laennec cirrhosis (three subjects) 3.3 to 6.1; Laennec cirrhosis (with hepatoma) 6.4; extrahepatic carcinoma with liver metastases, (three subjects) 8.5 to 11.0; Cruvellier-Baumgartner syndrome (clinical diagnosis) 10.9; carcinoma of head of pancreas with complete obstruction of long duration, 5.4.

22. Effect of Artificial Fever on Liver Function

Myers Hicks, M.D. *and* Byrd S. Leavell, M.D. (*introduced by J. Edwin Wood, Jr., M.D.*)

From the Department of Internal Medicine, University of Virginia Hospital, Charlottesville, Va.

The study was designed to determine the effect of artificially induced fever on liver function. Only subjects without evidence of liver disease were selected. The following tests were employed: bromsulfalein, cephalin-cholesterol, prothrombin time, icterus index, van den Bergh and plasma protein. Other observations included determination of temperature, pulse, blood pressure, skin temperature, hematocrit, hemoglobin, erythrocytes and leukocytes. Observations were made prior to induction of fever, during fever and within twenty-four hours after defervescence.

In ten patients twenty-two episodes of fever were induced by intravenous typhoid vaccine. Only the bromsulfalein test showed significant variation. In every instance when fever was present there was an increase in bromsulfalein retention. Values ranged from 4 per cent to 52 per cent above the control figure.

Three patients received pyrogenic doses of typhoid vaccine plus amidopyrine that prevented fever. Bromsulfalein retention was not observed.

In two patients three bouts of fever were induced by external heat. Bromsulfalein retention ranging from 4 per cent to 28 per cent occurred in each instance.

In ten afebrile subjects the bromsulfalein test was repeated using the same interval employed in the experiments outlined above. No increase in bromsulfalein retention was observed with this control procedure.

It is concluded that hyperpyrexia can be responsible for abnormal bromsulfalein retention in the blood. Further study is necessary to determine if the retention is due to hepatic dysfunction.

(*Read by Title*)

23. Electrophoretic Pattern in Myocardial Infarction

Preston Lowrance, M.D. (*introduced by Alfred Chanutin, M.D.*)

From the Department of Biochemistry, University of Virginia, Charlottesville, Va.

The plasma proteins of two patients with myocardial infarction have been studied at frequent intervals by means of electrophoresis. The abnormalities observed consisted of a slight depression of the albumin and an elevation of the alpha-1 and alpha-2 globulins and fibrinogin. The distribution of the protein components returned approximately to normal in one patient seven weeks after the infarct occurred. In the second patient, the alpha-2 globulin is still elevated four months after the infarction. There appears to be no direct correlation between the electrophoretic patterns and the changes in the sedimentation rate and the electrocardiogram. Patients with inactive rheumatic valvular disease served as controls and their protein distributions were within normal limits.

It has been shown by many investigators that any condition associated with tissue necrosis is accompanied by a decrease in albumin and an increase in alpha globulin fractions. These characteristic changes were observed in myocardial infarction and may therefore serve as an indicator of the state of the necrotic process in the infarcted myocardium.

24. Pharmacologic Studies on Myanesin

Arthur P. Richardson, M.D., James L. Morrison, M.D. *and* Harry A. Walker, M.D. (*introduced by Arthur J. Merrill, M.D.*)

From the Department of Pharmacology, Emory University School of Medicine, Atlanta, Ga.

Interest in alpha ethers of glycerine has been revived by the work of Bradley and Dewey in England, who have claimed that such compounds may be substituted for curare in connection with general anesthesia. We have found that myanesin, the most active of this series, possesses almost no curare-like action but rather it appears to be a very short acting basal anesthestic. By means of two chemical methods for determination of this compound in body fluids and tissues, it has been found that the compound disappears rapidly from the plasma and there is close correlation between plasma concentration and depressant action. It is distributed widely and occurs in high concentration in almost all tissues and body fluids. Highest concentration after continuous infusion are found in the brain and pancreas. It is apparently rapidly destroyed since less than 1 per cent can be recovered from bile and urine. The ultimate fate of the remainder has not been determined. The most important toxic reactions are: (1) sudden fall of blood pressure on rapid intravenous injection, probably due to direct myocardial depression and (2) local irritation which may result in thrombosis of vessels. Both cardiac depression and local tissue reaction are much less when dilute solutions are employed.

25. Comparison in Man of Serum Levels of Caronamide and Penicillin Following Multiple Doses of the Drugs

Manson Meads, M.D., Roland Long, M.D., Sherman Pace, M.D. (*by invitation*) *and* George Harrell, M.D.

From the Department of Medicine, Bowman Gray School of Medicine, Winston-Salem, N. C.

Seventeen ambulatory patients under sixty years of age without cardiac liver or kidney damage received 100,000 units of crystalline penicillin G intramuscularly every four hours for seven days. On the second, third and fourth days, carnomide simultaneously was administered orally to seven patients (Group A) in doses of 2 Gm. every four hours and to ten patients (Group B and C) in doses of 4 Gm. every four hours. One to three levels were determined daily. The samples of serum in Groups A and B were drawn four hours after the preceding dose and in Group C two hours after the preceding dose. The range of individual variation in caronamide and penicillin levels was great. When plotted, the mean value shows little effect of caronamide on penicillin levels in Group A. In Groups B and C the caronamide concentration increased steadily to the fourth day; the penicillin level reached a peak on the third day and remained there through the fourth day. The accumulation of caronamide in concentrations exceeding 20 mg. per cent in the serum is accompanied by a significant rise in serum penicillin level. Short interval or single dose studies have not disclosed this cumulative

effect. Mild toxic reactions were observed with caronamide levels exceeding 40 mg. per cent.

26. Dysfunction of the Adrenal Cortex in Cancer Patients

Edward C. Reifenstein, Jr., M.D., F. Homburger, M.D. *and* Konrad Dobriner, M.D. (*introduced by Albert Segaloff, M.D.*)

From the Departments of Clinical Investigation and Steroid Chemistry, the Sloan-Kettering Institute for Cancer Research, the Memorial Cancer Center, New York, N. Y.

Evidence will be presented which suggests that patients with cancer have dysfunction of the adrenal cortex. This evidence includes: (1) the nature of certain urinary steriod metabolites; (2) a comparison of the urinary steriod metabolites of cancer patients with those of patients with known disorders of the adrenal cortex; (3) a comparison of the "alarm reaction" following operation in patients with and without cancer; (4) the effect of adrenal cortical extract on the low liver glycogen content of patients with gastric cancer; (5) a comparison of electrolyte defects of patients with gastric cancer with those of patients with Addison's Disease and (6) a comparison of the adrenal cortical response to anterior pituitary adrenocorticotrophic hormone of patients with gastric cancer with those of patients with non-neoplastic non-adrenal diseases. The significance of these results will be discussed.

27. Daily Variability of the Fluid Restriction and Pitressin Concentration Tests for Renal Function

J. Maxwell Little, M.D. *and* George A. Anderson, M.D. (*introduced by Harold D. Green, M.D.*)

From the Department of Physiology and Pharmacology and Department of Internal Medicine, Bowman Gray School of Medicine, Winston-Salem, N. C.

Interpretation and comparison of the twelve hour fluid restriction and pitressin (10 units subcutaneously) concentration tests for renal function assumes that the daily variability in each is insignificant. This was tested in a random group of students, twenty-five (average six tests) with fluid restrictions and ten (average five tests) with pitressin.

The average *o* for the former was 2.9 and for the latter 3.8 units. There was no correlation between the individual mean values of specific gravity and *o*.

Interpreting specific gravities below 1.020 as impaired renal function, the results on the first fluid restriction and pitressin tests compared with subsequent tests were, respectively consistently good function 12, 2; consistently impaired function 2, 1; varying between good and impaired function 9,4; between impaired and good 2, 3 patients.

Interpreting specific gravities of 1.027 or greater as good, 1.014 to 1.027 doubtful, and below 1.014 impaired function, the respective results were: consistently good function 4,0; consistently doubtful 10,5; consistently impaired 0.0; varying from doubtful to good 8,3; poor to doubtful 2,2; poor to good 1,0. The pitressin test is more variable than the fluid restriction test. Because of daily variability, a single test of either type is of little value if the result indicates impaired or doubtful function.

28. Effect of the Adrenal Cortex on Diabetes during Infections

Louis Tobian, Jr., M.D. *and* Jack Edwards, M.D. (*introduced by Morton F. Mason, M.D.*)

From the Department of Pathological Chemistry, Southwestern Medical College, Dallas, Texas

The hypersecretion of the adrenal cortex caused by infections and the inhibition by adrenal cortical extracts of the hexokinase reaction of the diabetic muscle suggested that infections produced an exacerbation of diabetes by causing increased adrenal cortical secretion.

To study this, we divided a number of mice made diabetic with alloxan into two groups. One group had intact adrenals; the other group was adrenalectomized and then continuously given .05 cc. of Upjohn's lipo-adrenal cortex every eleven hours.

Both groups received three injections of typhoid vaccine, one every eight hours, and fasting blood sugars were obtained before and after the course of typhoid injections.

The adrenalectomized animals receiving adrenal cortex hormone showed as great a rise in blood sugar level after the typhoid vaccine as the animals with intact adrenals.

Hence, an increased secretion of adrenal cortex hormone after typhoid is not responsible for the exacerbation of the diabetes.

29. Dilution Acidosis

George T. Shires, M.D. *and* James Holman, M.D. (*introduced by Morton F. Mason, M.D.*)

From the Department of Pathological Chemistry, Southwestern Medical College, Dallas, Tex.

In studying the effects of the rapid saline administration upon circulation and respiration in the dog, a constant and progressive acidosis of arterial blood has been noticed. Apparently this phenomenon, although previously observed, has received no attention in recent literature. It was also demonstrated that this effect could be prevented by the simultaneous administration of bicarbonate in saline which was balanced to isotonicity.

The acidosis is interpreted as being the result of dilution of the total bicarbonate of the blood by pure saline. Since the CO_2 production of the body tissues remains relatively constant the H_2CO_3 numerator of the blood buffer H_2CO_3-$NaHCO_3$ remains relatively constant and with saline administration it is actually the $NaHCO_3$ which is diluted, altering pH toward acidity.

This concept should be kept in mind when saline administration is carried out, particularly in the face of existing acidosis or renal damage.

30. Phosphate Fractions in the Heart in Relation to Experimental Heart Failure

Gus G. Casten, M.D. (*introduced by Morton F. Mason, M.D.*)

From the Department of Pathological Chemistry, Southwestern Medical College, Dallas, Tex.

The important rôle played by the acid-soluble compounds of phosphorus in the chemistry of muscular contraction has prompted the following study of quantitative changes in these compounds in acute experimental heart failure.

The hearts of rats in which acute heart failure has been produced by a combination of hypervolemia and hyperthermia and by the use of the heart-lung preparation show well marked quantitative decreases in the adenosine triphosphate content.

Comparable animals, subjected to the same experimental procedures but in which cardiac fatigue is not produced, show no changes in the acid-soluble phosphorus compounds, including adenosine triphosphate and creatine phosphate.

31. Effect of Injection of Glucose into the Cerebrospinal Fluid

Robert W. Lackey, M.D. (*introduced by Arthur Grollman, M.D.*)

From the Southwestern Medical College, Dallas, Texas

It has recently been reported that injection of glucose into the cisterna magna in the dog and in man elicits changes in blood sugar level simulating those resulting from the intravenous administration of insulin. Since such a reaction would have important implications relative to regulation of carbohydrate metabolism, an attempt at corroboration has been made.

Each of six normal, fasted unanesthetized dogs were given by cisternal puncture 2 ml. of a 5 per cent solution of glucose following the withdrawal of an equal volume of cerebrospinal fluid. Blood sugar determinations were made before and at five, fifteen, thirty, sixty and 120 minutes following the injection. In no instance was a fall in blood sugar observed. Instead, the blood sugar level tended to rise slightly, the increase being more pronounced during the second hour.

The experiment was repeated with three dogs anesthetized with sodium pentobarbital with similar results.

32. Use of the Artificial Kidney

E. E. Muirhead, M.D. *and* John C. Vanatta, M.D. (*introduced by Arthur Grollman, M.D.*)

From the Southwestern Medical College, Dallas, Tex.

The application of the artificial kidney described by Kolff to nine nephrectomized and five normal dogs for one to three hours of dialysis resulted in death of the animals within a maximum period of forty-two hours, usually in less than twelve hours. These results indicate the technical difficulties in the procedure as described in the literature. The procedure, therefore, is not suitable for clinical application in its present status of development.

33. Antidiuretic Action of the Urine in Clinical Hypertension

Michael Ellis, M.D. (*introduced by Arthur Grollman, M.D.*)

From the Southwestern Medical College, Dallas, Texas.

In ten of thirteen patients with essential hypertension an antidiuretic substance has been

found in twenty-four hour urine samples. Studies have been made as to its nature, especially in respect to the posterior pituitary hormone, pituitrin.

34. Serologic Studies on Q Fever in the United States

Elias Strauss, M.D. (*by invitation*), S. Edward Sulkin, M.D. *and* (*by invitation*) Elizabeth L. Watson, M.D.

From the Departments of Bacteriology and Medicine, Southwestern Medical College, Dallas, Tex.

The present studies were undertaken to determine whether or not unrecognized Q fever is present in this country and, if so, to estimate its prevalence in different geographic areas and occupational groups. Complement-fixation tests were performed for the detection of serum antibodies against a yolk-sac antigen of *R. burneti* (Nine Mile strain).

The persistence of serum antibodies following natural infection was investigated. Serum specimens were obtained at intervals from individuals who were ill with naturally acquired Q fever in March, 1946. In most instances detectable antibodies, in high titer, were present eighteen months after infection.

Serum specimens were obtained from 1,400 employees of meat packing plants in a Southwestern city. Detectable complement-fixing antibodies were present in 8 per cent and significantly high titers were present in 2 per cent of these individuals. Another group of 1,000 serum samples was obtained from a Wassermann laboratory in the same geographic area. Of this number, 10 per cent had detectable serum antibodies and 1 per cent had significantly elevated titers. In a third group of 500 serum specimens obtained from a Wassermann laboratory in an Eastern city, only 1 per cent had detectable antibodies and none had significantly elevated titers.

These studies are continuing. The question of the specificity of low titers of antibodies has not been settled but it is clear that clinically unrecognized or inapparent infections with Q fever occur in this country. Preliminary observations suggest that occupation and possibly also geographic area may be factors in determining the prevalence of Q fever in the United States.

35. Hyaluronidase and Hyaluronic Acid of Group A Streptococci

Robert M. Pike, M.D. (*introduced by S. Edward Sulkin, M.D.*)

From the Department of Bacteriology and Immunology, Southwestern Medical College, Dallas, Tex.

Hyaluronidase activity of noncapsulated group A streptococci was detected by growing cultures in broth containing hyaluronic acid and testing the culture supernatant fluid for the mucoid polysaccharide. Of 110 strains, 55 per cent significantly reduced the hyaluronic acid content of the medium in twenty-four hours. When the period of incubation was prolonged to several days, additional strians were found to be hyaluronidase producers. Hyaluronidase could be detected in the culture fluid within the first few hours of growth, reached a maximum concentration near the end of the phase of most rapid growth and exhibited marked instability under various conditions.

Some strains of capsulated group A streptococci also destroyed, in one to seven days, hyaluronic acid present in the medium. This effect was evident not only on added hyaluronic acid but also on the mucoid polysaccharide produced in the culture. These strains, therefore, both produce and destroy hyaluronic acid but the hyaluronidase activity is weak in comparison with many non-capsulated strains.

No quantitative relationship was demonstrated between the amount of mucoid polysaccharide produced and virulence for mice. Neither did virulence of capsulated strains appear to be associated with the rate of disappearance of hyaluronic acid from the cultures.

36. Studies on the Pathogenesis of Rheumatic Fever

Gladys J. Fashena, M.D., Robert M. Pike, M.D. (*by invitation*) *and* S. Edward Sulkin, M.D.

From the Departments of Pathology, Pediatrics and Bacteriology, Southwestern Medical College, Dallas, Tex.

Antirat heart rabbit sera have been prepared by the injection of rat-heart emulsions into rabbits, with and without the use of the Freund adjuvant. Antibodies to rat-heart and to rat serum were demonstrated by the precipitin test and the collodion particle agglutination technic. Serum antibodies were absorbed from some of

the immune sera by *in vitro* and *in vivo* methods. Young rats were given a series of injections of the immune sera. Control animals received similar injections of (1) normal saline; (2) normal rabbit serum and (3) diluted egg albumin. The animals were sacrificed after varying intervals and the hearts examined histologically. Rheumatic-like lesions consisting of (1) edema and cellular proliferation in heart valves; (2) focal cellular accumulations in the valve ring and (3) focal degenerative changes in the ground substance of the valve ring connective tissue, surrounded by a few mononuclear cells, were detected in many of the animals receiving protein-containing injections but not in the saline-treated controls. These lesions appear to represent a response to foreign protein rather than to specific anti-organ antibodies.

37. Comparative Effects of Hypertonic Solutions of Various Inorganic and Organic Sodium Salts, Glucose and Plasma Protein upon the Volume of the Brain of Anesthetized Dogs

F. W. Klinge, M.D., M. Leven, M.D. (*by invitation*) *and* Carl A. Moyer, M.D.

From the Department of Surgery, Southwestern Medical College, Dallas, Texas.

Changes in brain volume attending the intravenous injection of the above hypertonic solutions were observed continuously for periods of eight to eighteen hours. A water-manometer attached to a closed elastic system which was held in place over both cerebral hemispheres by an air-tight artificial lead skull plate was used as the recording system.

The concentration of sodium in all the solutions of sodium salts employed was 1,185 mEq. per liter of water. These solutions were injected intravenously at a rate that was sufficiently slow to obviate the transitory depression of arterial blood pressure that follows the rapid injections of hypertonic solutions. A dose of 4.03 ml. per Kg. of body weight was uniformly employed.

It was found that sodium succinate produced a greater and more prolonged reduction in brain volume than did sodium lactate; racemic sodium lactate was more effective than sodium chloride and sodium chloride was usually more effective than a mixture of sodium chloride and bicarbonate. No secondary increases of the brain volume above the control level were seen following the injection of the above salts.

A 25 per cent solution of salt-poor human albumin given in doses of 6 Gm. of albumin per Kg. of body weight had no effect upon the volume of the brain during the injection period; during the postinjection period the volume of the brain usually increased.

Transient, small reductions of intracranial volume followed the injection of a 25 per cent solution of glucose in water (dosage of 4 to 6 cm. per Kg.). An increase in intracranial volume above the initial levels usually followed the initial reduction.

No correlation could be found between the effects upon the volume of the brain of the above mentioned substances and the simultaneous changes in the blood pressure, the body temperature, the load of water or the rate of urine flow.

The differences between the actions of the various sodium salts cannot be attributed to variations in effective osmolar concentration of the solution employed; it seems probable that the characteristics of the anion may be responsible for them.

Book Reviews

The Principle and Practice of Medicine. By Henry A. Christian, M.D. 16th Edition. Pp. 1539. New York, 1947. D. Appleton-Century. *Price* $10.00.

In these days of specialization and laboratory evaluation, when medical practice leans toward a highly scientific appraisal of physiologic and anatomic disturbances now increasingly subject to more exact diagnosis and when therapy is rational and subjected to the law of controls, the medical student or practitioner of medicine not infrequently finds himself beset on the one hand by the cries of the expert urging him into more and more detailed and expensive workups for his patients and, on the other hand, by the five-minute history, physical and prescription writing type of consultation (so frequently dictated by the necessities of time and economies) but happily now belonging to a disappearing medical era. In this quandary it is refreshing to have recourse to a medical textbook cognizant of each extreme and presenting in a readable fashion a mature synthesis based on the wise judgment of such a seasoned and competent teacher as Dr. Henry A. Christian.

"The Principles and Practice of Medicine" first appeared in 1892 under the hand of Sir William Osler and has been edited since 1938 by Dr. Henry A. Christian. The present 16th edition continues the fine tradition of its noteworthy past.

The subject material is subdivided with an etiologic breakdown when possible; when not, into systemic diseases. No significant omissions were noted by this reviewer. Each topic is further separated by special headings for etiology, pathology, symptoms, diagnosis and treatment. An adequate list of pertinent and up-to-date references is consistently presented. The typography is satisfactory although those who appreciate illustrations will find none. An excellent 156 page index, a table of normal laboratory values and a history of medicine from 1892 to 1947 add to the usefulness of the volume.

This, then, is a medical textbook in keeping with its distinguished tradition.

F. K. H.

Diseases of the Nose and Throat. By Charles J. Imperatori, M.D. 3rd Edition. Pp. 576, with 480 illustrations. Philadelphia, 1947. J. B. Lippincott Company. *Price* $12.00.

This is the third edition of a well known text book. Diseases of the nose and throat are presented in a clear, concise and practical manner. Office procedure and treatment are discussed in detail. This is followed by a complete description of the pathology. There are 480 excellent illustrations, many of which show the microscopic anatomy of the disease under discussion. Treatment has been brought up to date by revision of chapters to include the newer advances of chemotherapy and radiotherapy. Dr. Ira I. Kaplan has written the chapter on Radium and Roentgen Ray. Dr. Andrew A. Eggston has written the chapter on Laboratory Aids. The experience of the authors make this an authoritative work. It can be recommended as a textbook for students and as a reference work for the practicing physician.

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*After treatment of "some 500 patients with chronic arthritis over a period of eight years," these conclusions about Ertron-Steroid Complex, Whittier, were reached in a leading clinic for the study and treatment of arthritis.**

"The medication is a relatively nontoxic therapeutic agent, and is beneficial in the treatment of chronic arthritis of the rheumatoid type.

Intolerance occasionally occurs but is easily controlled by reducing the dosage or discontinuing the medication temporarily.

Demonstrable signs of improvement are definitely noted, and are frequently sustained even after cessation of medication.

There is no increase of calcification of the blood vessels observed either roentgenologically or by ophthalmological examination of the retinal vessels.

The renal function is not impaired, as was demonstrated by urinalysis and nonprotein nitrogen determinations."

The Uses of Vitamins in the Treatment of Chronic Arthritis; Traeger, C.H.; The Medical Clinics of N. Am. 30:616 (May) 1946.

ERTRON is a Registered Trade Mark of Nutrition Research Laboratories

RESEARCH

Each capsule of Ertron contains 5 milligrams of activation-products having antirachitic activity of 50,000 U.S.P. units. Biologically standardized.

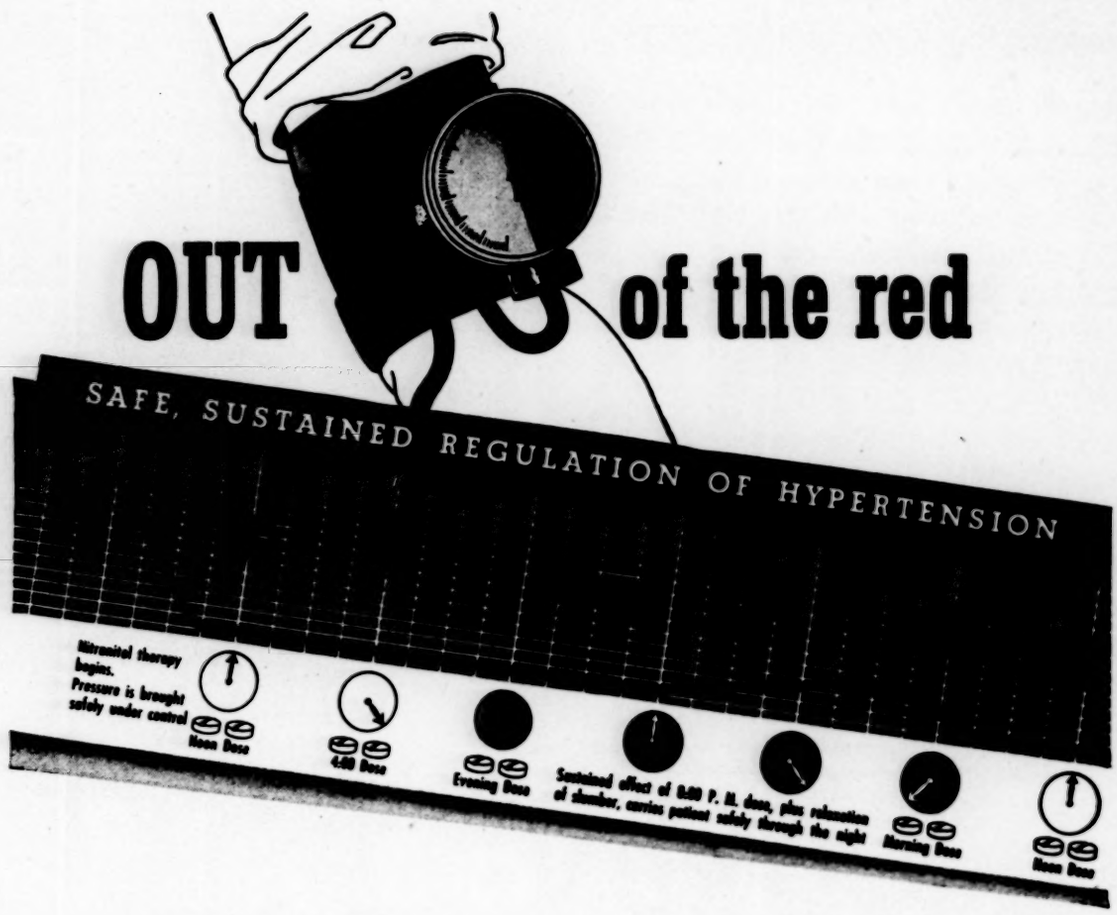
ERTRON

Each ampule of Ertron Parenteral contains 1 cc of activation-products having antirachitic activity of 500,000 U.S.P. units in sesame oil. Biologically standardized. Combined oral and parenteral therapy is an effective measure of patient control by the physician.



NUTRITION RESEARCH LABORATORIES

CHICAGO



Vasorelaxation produced by Nitranitol is GRADUAL, avoiding the dangerously abrupt blood pressure fluctuations of the quick-acting drugs.

The hypotensive effect of Nitranitol is PROLONGED, each dose overlapping the one before—permitting maintenance of a relatively constant pressure.

The negligible clinical toxicity of Nitranitol, making it SAFE for use over an indefinite period, is in contrast to the cumulative toxicity of the thiocyanates.

Gradual, Prolonged, Safe Vasodilation with

NITRANITOL

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Nitranitol contains ½ gr. mannitol hexanitrate in each scored tablet. Dosage is 1 to 2 tablets every four hours. Available in hospital and prescription pharmacies in bottles of 100 and 1000.

For cases requiring sedation in addition to vasodilation.
NITRANITOL WITH PHENOBARBITAL
Each scored tablet contains ½ gr. mannitol hexanitrate and ¼ gr. phenobarbital. Bottles of 100 and 1000.

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THE WM. S. MERRELL COMPANY
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Announcing

MICROPELLETS PROGYNON

(aqueous suspension, alpha-estradiol)

a new departure in estrogen therapy



MICROPELLETS PROGYNON provide a unique and completely new technic for parenteral administration of pure alpha-estradiol. For the first time it has become possible to suspend the primary follicular hormone in the form of MICROPELLETS in normal saline. Prolonged and constant absorption from a semipermanent depot is established in the tissues by a simple intramuscular injection. Where injections of an oil solution are not feasible or desirable, a single injection of 1 mg. of MICROPELLETS PROGYNON may be substituted in order to achieve prolonged control.

MICROPELLETS PROGYNON offer economy in estrogen therapy while providing the complete safety and freedom from side effects inherent in natural hormones.

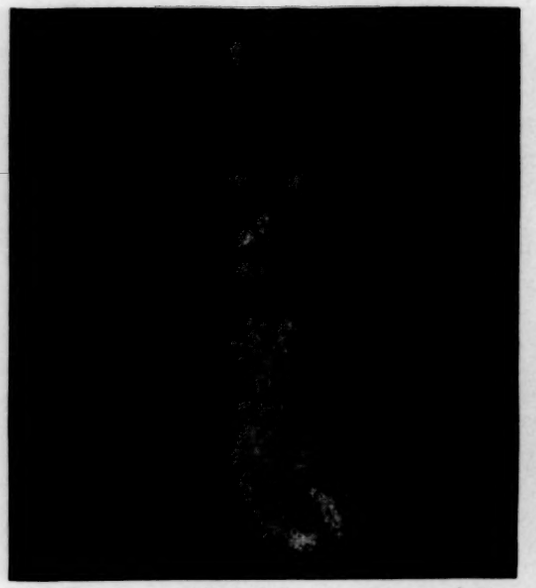
MICROPELLETS PROGYNON are available in multiple dose vials of 10 cc., each cubic centimeter containing 1 mg. of pure alpha-estradiol (12,000 R.U. or 120,000 I.U.). Boxes of 1 and 6 vials.

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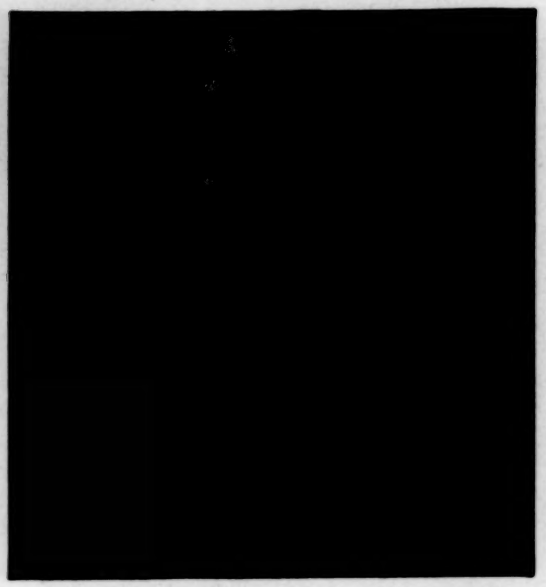


Chronic osteomyelitis following compound fractures of leg twelve years before. Fourteen surgical procedures had failed to close the cavity. Pain and foul-smelling discharge from sinus caused patient to request amputation. (*Above*) appearance of lesion following saucerization.

Treatment with Chloresium Solution (Plain) daily for first two weeks, then Chloresium Ointment every other day. Cavity showed progressive closure, purulent drainage ceased. Pinch grafts of granulation tissue at base were successful and cavity closed completely. No subsequent breakdown.

CHLOROPHYLL THERAPY—

. . . accelerates healing
. . . stimulates normal cell growth
. . . controls superficial infection
. . . reduces scar formation
. . . is nontoxic—bland and soothing
. . . deodorizes malodorous lesions



Reports from clinicians emphasize the effectiveness of Chlorophyll Therapy as made possible by Chloresium

BOEHME, E. J.	The Treatment of Chronic Leg Ulcers with Special Reference to Ointment Containing Water-Soluble Chlorophyll.	The Lahey Clinic Bulletin, 4: 242 (1946)
BOWERS, WARNER F.	Chlorophyll in Wound Healing and Suppurative Disease.	Amer. J. Surgery, LXXIII: 37 (1947)
GAHAN, E., KLINE, P.R. and FINKLE, T.H.	Chlorophyll in the Treatment of Ulcers.	Arch. Dermat. & Syph. 47: 849 (1943)
HOLMES, G. W. and MUELLER, H. P.	Treatment of Post-Irradiation Erythema with Chlorophyll Ointment.	Am. J. Roentgenol. 50: 210 (1943)
LANGLEY, W. D. and MORGAN, W. S.	Chlorophyll in the Treatment of Dermatoses.	Penn. Med. Journal Vol. 51; No. 1 (1947)
MORGAN, W. S.	Chlorophyll Therapy A Review of 114 cases.	Guthrie Clinic Bulletin, 16: 94 (1947)
SMITH, L. W. and LIVINGSTON, A. E.	Chlorophyll: An Experimental Study of Its Water-Soluble Derivatives in Wound Healing.	Am. J. Surg. New Ser. LXII: 358 (1943)

Chloresium

Natural, nontoxic therapeutic chlorophyll preparations.
Available at leading drug stores

FREE! Complete literature and clinical samples of Chloresium Solution (Plain), Ointment and Nasal Solution will be sent upon request. Address Dept. JM-3.

RYSTAN COMPANY, Inc.
7 N. MacQuesten Pkwy., Mt. Vernon, N.Y.
SOLE LICENSEE — LAKELAND FOUNDATION

NOW...a New, Effective ANTIHISTAMINIC of Low Toxicity

Clinical studies have established Neo-Antergan Maleate (brand of pyranisamine maleate) as an efficient antihistaminic drug of relatively low toxicity, effective in preventing or relieving symptoms in a high percentage of patients with certain allergic manifestations.

Neo-Antergan has proved to be most effective in the following conditions:

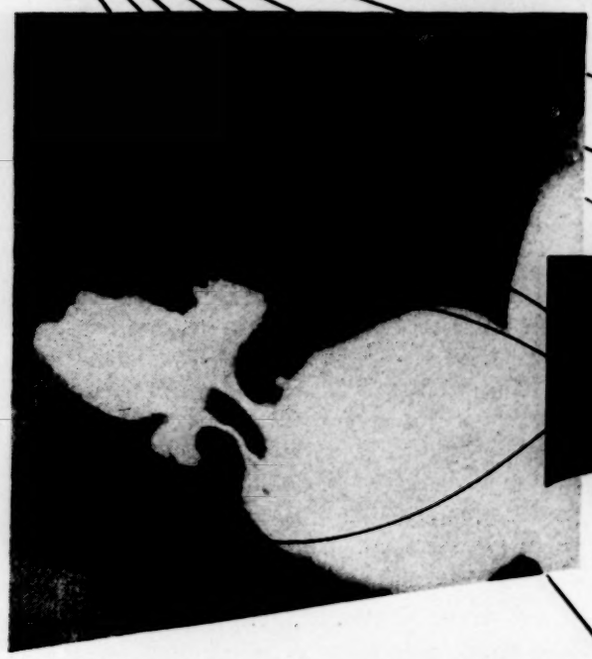
URTICARIA • HAY FEVER • ALLERGIC DRUG REACTIONS • VASOMOTOR RHINITIS PRURITUS • ATOPIC DERMATITIS AND ANGIONEUROTIC EDEMA.

Beneficial results are obtained also in bronchial asthma and eczema, but in a lower percentage of cases. Certain cases of migraine, presumably those due to histamine or a histaminelike substance, and some cases of abdominal pain thought to be caused by smooth muscle spasm induced by allergic phenomena, also may be expected to respond in varying degree to treatment with Neo-Antergan. The action of Neo-Antergan is palliative, not curative.

Undesirable reactions are generally mild and transient, although moderately severe side effects have been observed in a relatively small percentage of cases. It is rarely necessary to discontinue treatment with Neo-Antergan because of toxic reactions.



A NEW, MORE COMPLETE APPROACH IN



Peptic Ulcer

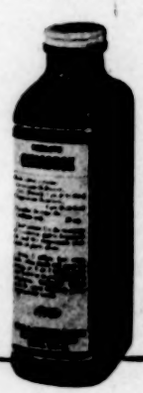
Cimadrox provides a new and effective approach to the treatment of peptic ulcer, chronic gastritis and gastric hyperacidity. It supplies not only the established antacid properties of magnesium trisilicate and aluminum hydroxide, but also the desirable influence of ascorbic acid.

Recent evidence indicates that the typical ulcer dietary is deficient in a number of essential nutrients, particularly vitamin C. Administration of adequate quantities of this vitamin restores the ascorbic acid blood level and hastens healing of the ulcer.

The acid-neutralizing influence of Cimadrox is profound and sustained. Since its antacids are of the nonsystemic type, it cannot lead to alkalosis or to acid rebound. The presence of magnesium trisilicate is especially advantageous since this compound forms gelatinous silica on reacting with hydrochloric acid, thus providing a protective medium for the ulcer crater.

Cimadrox leads to prompt and prolonged relief of epigastric distress and pain in gastric and duodenal ulcer, in gastric hyperacidity and in chronic gastritis. Each Cimadrox tablet provides 6 gr. magnesium trisilicate, 3 gr. aluminum hydroxide and 20 mg. ascorbic acid as the sodium salt. Tablets should be thoroughly chewed.

In bottles of 1000, 500, and 100 tablets



THE S. E. MASSENGILL COMPANY
Bristol, Tenn.-Va.
NEW YORK · SAN FRANCISCO · KANSAS CITY

SEMCO

TABLETS

Cimadrox

NONSYSTEMIC ALKALIES *plus* VITAMIN C

74%

...L RESULTS
in common urinary tract infections



Mandelamine* therapy affords notably successful results in a high percentage of common urinary tract infections. Carroll and Allen,† in their recent carefully analyzed study of 200 unselected cases, obtained prompt and effective responses in 74 per cent of the patients.

Mandelamine **therapy offers 6 advantages.**

1. No gastric upset;
2. No fluid regulation;
3. No dietary restrictions;
4. No supplementary acidification (except when urea-splitting organisms are present);
5. Wide range of antibacterial action;
6. Simplicity of administration.

MANDELAMINE

Reg. U. S. Pat. Off.

Brand of Hexydaline

(*Methenamine Mandelate*)

SUPPLIED: Enteric-coated tablets of 0.25 Gm. (3¾ grains) each, in packages of 120 tablets sanitaped, and in bottles of 500 and 1,000.

*The word MANDELAMINE is a registered trademark of Nepera Chemical Co., Inc.

†Carroll, G., and Allen, H. N.: The Treatment of Urinary Infections with Mandelamine (Methenamine Mandelate); A Clinical Study of 200 Cases. J. Urol. 55: 674-681 (June) 1946.

NEPERA CHEMICAL CO., INC.

Manufacturing Chemists

NEPERA PARK **YONKERS 2, N. Y.**

in weight reduction— new evidence of the efficacy of Dexedrine

Excerpts from a recent study entitled, THE MECHANISM OF AMPHETAMINE-INDUCED LOSS OF WEIGHT: A Consideration of the Theory of Hunger and Appetite —by Harris, S. C.; Ivy, A. C., and Searle, L. M.: J. A. M. A. 134:1468 (Aug. 23) 1947.

experiment 1. Does 'Dexedrine' Sulfate, by controlling appetite, decrease food intake and body weight in human subjects?

results ". . . our obese subjects lost weight when placed on a diet which allowed them to eat all they wanted three times a day . . ."

experiment 4. Does the rather prolonged administration of Dexedrine cause any evidence of disturbance of tissue functions?

results "No evidence of toxicity of the drug as employed in these studies was found . . . no evidence of deleterious effects of the drug was observed."

Dexedrine* Sulfate

(dextro-amphetamine sulfate, S.K.F.) Tablets Elixir

for control of appetite in weight reduction

* T.M. REG. U.S. PAT. OFF.

Smith, Kline & French Laboratories, Philadelphia